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Title: Comparison of Kaposi sarcoma risk in HIV-positive adults across five continents: a multiregional multicohort study

Running head: Regional KS risk in HIV-positive adults

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Key words: Kaposi sarcoma; HIV; antiretroviral therapy; cohort study

Summary: Men and women in South Africa and men who have sex with men remain at increased risk of developing Kaposi sarcoma compared with other HIV-positive persons who initiated antiretroviral therapy, likely due to high human herpesvirus 8 coinfection rates.

Abstract (word count: 250)

Background: We compared Kaposi sarcoma (KS) risk in adults who initiated antiretroviral therapy (ART) across the Asia-Pacific, South Africa, Europe, Latin, and North America.

Methods: We included cohort data of HIV-positive adults who initiated ART after 1995 within the framework of two large collaborations of observational HIV cohorts. We present incidence rates and adjusted hazard ratios (aHRs).

Results: We included 208,140 patients from 57 countries. Over 1,066,572 person-years (pys) 2,046 KS cases were diagnosed. KS incidence rates per 100,000 pys were 52 in the Asia-Pacific, and ranged between 180 and 280 in the other regions. KS risk was five times higher in South African women (aHR 4.56, 95% confidence intervals [CI] 2.73-7.62) and two times higher in South African men (aHR 2.21, 95% CI 1.34-3.63) compared to their European counterparts. In Europe, Latin, and North America KS risk was six times higher in men who have sex with men (MSM, aHR 5.95, 95% CI 5.09-6.96) than in women. Comparing patients with current CD4 cell counts ≥700 cells/µl to those with CD4 counts <50 cells/µl, KS risk was halved in South Africa (aHR 0.53, 95% CI 0.17-1.63), but reduced by ≥95% in other regions.

Conclusions: Despite important ART-related declines in KS incidence, men and women in South Africa and MSM remain at increased KS risk, likely due to high human herpesvirus 8 coinfection rates. Early ART initiation and maintaining high CD4 cell counts are essential to further reduce KS incidence worldwide, but especially in Southern Africa additional measures might be needed.

Introduction

People infected with human immunodeficiency virus (HIV) are at high risk of developing Kaposi sarcoma (KS) [1], and this risk appears to vary geographically. KS incidence rates seem to be higher in adults who initiated antiretroviral therapy (ART) in sub-Saharan Africa [2,3] and the US [4] than in Europe [5]. However, direct comparisons of KS incidence rates across studies are complicated by differences in study populations and designs.

Several factors could contribute to regional differences in KS risk, including differences in the HIV epidemic, the adequacy of local health care, and the prevalence of human herpesvirus 8 (HHV-8). HHV-8 is a necessary but not sufficient cause of KS [6], and its distribution varies by geographic region and population group [7]. HIV-related immunosuppression is a strong risk factor for KS in HHV-8 coinfected persons [5,8–10]. Access to health care varies across regions, and patients in high-income countries initiate ART at higher CD4 cell counts than patients in low- and middle-income settings [11].

We compared KS incidence rates in HIV-positive adults who initiated ART across different continents, and assessed factors associated with regional differences in KS risk.

Methods

Databases

We analyzed longitudinal routine clinical care data of HIV-positive patients within the framework of the International epidemiology Databases to Evaluate AIDS (IeDEA) and the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. IeDEA is a global research consortium of observational HIV cohorts with data

centers in the Asia-Pacific, Australia, Africa, North, and Latin America. Four IeDEA regions contributed data to this study: the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) [12], the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) [13], IeDEA Southern Africa [14], and IeDEA Asia-Pacific[15]; the latter includes data from two geographical regions: the Asia-Pacific and Australia. COHERE in EuroCoord is a collaboration of observational HIV cohorts across Europe [16]. For details on how data were collected and combined, see Supplementary box S1. All cohorts obtained ethical approval from local ethics committees or institutional review boards.

Inclusion criteria and definitions

We restricted the analysis to cohorts that systematically collected cancer data or had improved their data through record linkages with cancer registries. We included HIV-positive adults (≥16 years) who initiated ART after enrolment into cohort from 1996 onward. We excluded patients without follow-up after ART initiation, and patients with no CD4 measurements under follow-up. We excluded regions with <500 eligible patients and cohorts with <100 eligible patients. We excluded the region Asia-Pacific from statistical models due to few KS cases (post-hoc decision). Incident KS cases were defined as histologically or clinically diagnosed KS at any time after ART initiation. ART was defined as a regimen of at least three antiretroviral drugs from any class, including protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors, and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Patients were assumed to remain on ART once initiated. CD4 counts at ART initiation were defined as the measurement nearest to ART initiation within 180 days before to seven days after initiation. The HIV/AIDS stage at ART initiation was defined according to the US Centers for Disease Control and Prevention (CDC) [17].

Statistical analyses

We calculated raw KS incidence rates by dividing the number of incident KS cases by person-years (pys) at risk. Time at risk was measured from ART initiation to the first occurrence of KS diagnosis, last follow-up visit, death, or database closure. We anticipated that the KS hazard would vary by follow-up time and geographic region and used proportional hazard flexible parametric survival models [18] to compare the risk of developing KS after ART initiation across regions and to identify KS risk factors. We modeled the baseline hazard using restricted cubic splines with four degrees of freedom and allowed for time-dependent region-effects with two degrees of freedom. Likelihood ratio tests were used to test for interactions between risk factors and regions. We assessed gender, exposure group (women, heterosexual men, MSM), age at ART initiation (16-25, 26-35, 36-45, 46-55, ≥56 years), first-line ART regimen (NNRTI-based, PI-based, other), calendar period of ART initiation (1996-1998, 1999-2003, 2004-2007, 2008-2014), and current (time-updated) CD4 cell count (<50, 50-99, 100-199, 200-349, 350-499, 500-699, ≥700 cells/µl). Mode of infection, HIV/AIDS stage, and HIV RNA at ART initiation were assessed in descriptive analyses.

We fit "crude" models with one risk factor and its interaction with region (where applicable) to compare the actual KS burden across regions. Adjusted models with relevant risk factors and their interaction with region (if necessary) were then fit to assess remaining differences in KS incidence rates across regions. The main adjusted model included region, gender and its interaction with region, age at ART initiation and its interaction with region, current CD4 count and its interaction with region, first-line ART regimen, and calendar period of ART initiation. The second adjusted model was restricted to the three regions with data on sexual orientation, Europe, Latin, and North America, and included exposure group, age at ART

initiation, current CD4 cell count, first-line ART regimen, and calendar period of ART initiation. In sensitivity analyses, we excluded the first three months of follow-up. KS incidence rates were predicted from adjusted models for patients with a standardized risk factors set: initiation of NNRTI-based regimens between 2008-2014 at the age of 40 years and current CD4 cell count between 350-499 cells/µl. Results are presented as medians with interquartile ranges (IQR), number and percentages of patients, incidence rates per 100,000 pys and hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were done using Stata 14 (Stata Corporation, College Station, Texas, USA) and R (R Foundation, Vienna, Austria).

Results

Descriptive analyses

The merged multiregional dataset included data on 408,395 HIV-positive adults. We excluded 200,255 patients for reasons detailed in Supplementary figure S1. Excluded and included patients were similar with regard to gender (men 70% vs. 69%), risk group (MSM 33% vs. 36%), age (median 35 vs. 37 years), and CD4 count at ART initiation (median 240 vs. 222 cells/µl).

We included data on 208,140 patients from 42 cohorts in 57 countries across the Asia-Pacific, South Africa, Europe, Latin, and North America (Figure 1). Median age at ART initiation was 37.3 years (IQR 31.4-44.4) and similar across regions (Table 1). The percentage of men ranged from 37% in South Africa to 75% in North America. More men were MSM in Europe (54%), Latin America (57%), and North America (67%), though not in the Asia-Pacific (34%); data were not available for South Africa. Median CD4 cell count at ART initiation was <200 cells/µl

in the Asia-Pacific, South Africa, and Latin America, and >200 cells/µl in North America and Europe (Table 1). In South Africa and the Asia-Pacific, <5% of patients initiated ART before 2004, but 39% in Europe and 63% in North America initiated ART between 1996 and 2003. Approximately half of North American and European patients initiated PI-based regimens, whereas 22% in Latin America, and <10% in South Africa and the Asia-Pacific received PI-based regimens. Median follow-up after ART initiation was >4 years in Europe, North, and Latin America, but shorter in the Asia-Pacific (2.7 years) and South Africa (2.0 years).

Over 1,066,572 pys, 2,046 KS cases were diagnosed (Europe: 1,572; North America: 211, South Africa: 150, Latin America: 109; Supplementary table S1). Median time between ART initiation and KS diagnosis was 0.5 years (IQR 0.1-2.5). Median age at KS diagnosis ranged from 35 years in the Asia-Pacific to 43 years in North America. Median CD4 cell count at KS diagnosis was <100 cells/µl in the Asia-Pacific, Latin, and North America, and 180 cells/µl in South Africa and Europe.

The raw KS incidence rate per 100,000 pys was highest in South Africa (280, 95% CI 238-328), followed by Latin America (244, 95% CI 203-295), North America (237, 95% CI 207-271), Europe (180, 95% CI 172-190), and the Asia-Pacific (52, 95% CI 19-137; Supplementary table S2). The raw KS incidence rates were especially high in patients with current CD4 counts <50 cells/µl (ranging from 1,368 in South Africa to 2,950 in Latin America; Supplementary table S3); MSM in Europe, Latin, and North America (all >300), and South African men (371, 95% CI 293-470; Supplementary table S4).

Risk factors for incident KS

The following statistical models include the regions Europe, South Africa, Latin, and North America. Crude KS incidence rates were highest immediately after ART initiation and declined

steeply thereafter in all population groups (Supplementary figures S2, S3). The effect of gender, age at ART initiation, and current CD4 cell count on KS risk varied across regions. In all regions, women had a lower risk of developing KS than men in crude and adjusted analyses, but the gender difference was less pronounced in South Africa (p-value for interaction <0.001; Table 2, Figure 2). In Europe, North, and Latin America, KS incidence rates were highest in MSM, followed by heterosexual men, and women in crude and adjusted analyses (Supplementary figure S4). After adjusting for current CD4 count, age at ART initiation, first-line regimen, and calendar year of ART initiation, the KS risk was 53% higher in heterosexual men than women (adjusted HR [aHR] 1.53, 95% CI 1.28-1.83), and six times higher in MSM (aHR 5.95, 95% CI 5.09-6.96). There was no evidence that the effect of exposure group on KS risk differed across regions (p-value for interaction, 0.19).

In all regions, KS risk was highest in persons with current CD4 cell counts <50 cells/µl. However, comparing patients with current CD4 cell counts ≥700 cells/µl to those with cell counts <50 cells/µl, KS risk was halved in South Africa (aHR 0.53, 95% CI 0.17-1.63), but reduced by ≥95% in the other regions (p-value for interaction <0.001; Figure 3). In Europe and North America, KS risk tended to increase with older age, whereas it decreased in Latin America and South Africa (p-value for interaction, 0.003; Table 2). There was no strong evidence that the effect of first-line regimen or calendar period of ART initiation varied across regions (Supplementary table S5). Patients who received PI-based first-line regimens had a slightly higher risk of developing KS than patients who received NNRTI-based regimens (aHR 1.12. 95% CI 1.01-1.24).

Comparison of KS risk between regions

In women, KS risk at two years after ART initiation was more than three times higher in South Africa than in Europe in crude analyses (HR 3.19, 95% CI 2.26-4.52) and almost five times higher in analyses adjusted for current CD4 count, age at ART initiation, first-line regimen, and calendar period of ART initiation (HR 4.56, 95% CI 2.73-7.62, Table 3). The adjusted KS risk tended to be lower in North, and Latin American women than in European women, but the effect was not statistically significant. In men, the crude risk of developing KS was highest in North America compared with Europe (HR 1.65, 95% CI 1.35-2.01), followed by South Africa (HR 1.44, 95% CI 1.03-2.00). In adjusted analyses, the HR for men declined to 0.75 (95% CI 0.44-1.27) in North America, but it increased to 2.21 (95% CI 1.34-3.63) in South Africa. Both changes were mainly due to adjustment for current CD4 count. KS risk did not differ significantly between Latin American and European men in crude or adjusted analyses.

We predicted KS incidence rates per 100,000 pys at two years after ART initiation for patients with current CD4 counts of 350-499 cells/µl who initiated NNRTI-based regimens between 2008-2014 at the age of 40 years. Predicted KS incidence rates in women were 12 (95% CI 4-36) in Latin America, 14 (95% CI 7-29) in North America, and 28 (95% CI 22-36) in Europe. In heterosexual men, KS incidence rates were 29 (95% CI 20-42) in Latin America, 35 (95% CI 27-47) in North America, and 34 (95% CI 27-41) in Europe. In South Africa, KS incidence rates remained at 212 (95% CI 131-344) in men and 129 (95% CI 80-208) in women. Predicted KS incidence rates in MSM were 114 (95% CI 81-160) in Latin America, 131 (95% CI 109-157) in Europe, and 138 (95% CI 107-178) in North America (Supplementary table S6).

Sensitivity analysis

Excluding the first three months of follow-up resulted in lower raw KS incidence rates (Supplementary table S7); other results remained similar (Supplementary tables S8-S10).

Discussion

After adjustment for HIV-related risk factors, HIV-positive men and women in South Africa had a higher risk of developing KS than their counterparts in Europe. In Europe, Latin, and North America, MSM had a higher KS risk than heterosexual men and women. In all regions, current CD4 cell count <50 cells/µl was a strong risk factor for incident KS. However, the clear trend towards lower KS risk with higher current CD4 counts seen in Europe, North, and Latin America was not observed in South Africa.

This is the first study to directly compare KS risk across several continents in adults who initiated ART. We used the same inclusion criteria, definitions, and statistical methods across regions. However, comparability of incidence estimates might be impaired by regional and cohort-level differences in mode and completeness of KS ascertainment. We assumed that patients within regions were independent, which might have led us to overestimate the precision of regional KS risk comparisons. To reduce under-reporting of KS, data from South Africa were restricted to two urban cohorts that obtained additional KS data through record linkages with a cancer registry [2]. However, these South African data are not necessarily representative for the whole of South Africa, and it is unclear to what extent these results can be extrapolated to Southern Africa as a region. We did not consider ART interruptions and, therefore, KS risk in patients continuously on ART might be lower than what we found in our

analysis for patients after ART initiation. Most patients from North America initiated ART before 2004 with NNRTI or PI-based regimens, whereas almost all patients in South Africa initiated NNRTI-based ART from 2004 onward. Temporal changes in ART effectiveness and HIV care in general might contribute to the observed regional differences in KS risk. HIV RNA measurements at ART initiation were missing for 30% of patients in Latin America and 78% in South Africa. Therefore, it was not possible to use HIV RNA measurements to assess ART response and treatment failure. Patient-level data on HHV-8 serostatus, immune reconstitution inflammatory syndrome (IRIS)-KS, and mode of KS ascertainment were generally not available.

In our analyses, KS incidence rates were highest immediately after ART initiation, which is consistent with previous studies [4,5,10,19]. These peaks are partly explained by immunodeficiency that persisted after initiating ART, unmasking IRIS-KS [9,20], and possible misclassification of some prevalent KS as incident KS. However, when we excluded KS cases occurring within three months after ART initiation in sensitivity analyses, our results remained similar. The effect of age at ART initiation differed across regions with KS risk increasing with older age in North America and Europe, but decreasing in Latin America and South Africa. Most previous studies have shown no or only a weakly positive association between older age and KS risk in patients on ART [3–5,8,9,19,21]. The slightly increased KS risk in patients who received PI-based first-line regimens might be due to confounding by indication.

Our study is one of the first to report KS incidence rates in HIV-positive adults in the Asia-Pacific, a region where HHV-8 prevalence is generally low [22]. Compared to the other regions, we found KS risk to be much lower in the Asia-Pacific. KS incidence rates were higher in South African than in European men and women. Previous studies also tended to show

higher KS incidence rates in HIV-positive persons in sub-Saharan Africa [23,24], where HHV-8 is endemic, than in Europe [9,21]. As in other studies, our analyses showed higher KS incidence rates in MSM than in heterosexual men [5,8,25], and higher KS risk in men than in women [19,25]. In South Africa, the gender difference in KS risk was smaller than in other regions. This pattern may reflect different HHV-8 risk profiles in HIV-positive men and women. In Europe, Latin, and North America, >50% of included men were MSM and, therefore, at high risk of HHV-8 coinfection, whereas women in these regions generally have lower HHV-8 seroprevalence [7]. In sub-Saharan Africa where HHV-8 is endemic, both men and women are at high risk of HHV-8 coinfection [26]. Indirect effects of sex hormones on KS tumorigenesis [27] and gender differences in immune response might also contribute to the male predominance in KS risk.

The high KS risk in South African compared with European women might be mainly explained by the higher HHV-8 prevalence in South African compared with European women. However, South African men also had a higher risk of developing KS than European men after adjustment for HIV-related factors. Besides differences in HHV-8 prevalence other factors like environmental exposures and malaria might play a role [28–30]. However, such co-factors for KS pathogenesis remain controversial. Our analyses also suggest that differences in access to HIV treatment and patient monitoring contribute to the regional differences in KS risk. For example, North American men had a higher risk of developing KS than European men, but after adjusting for current CD4 cell counts, the KS risk was similar.

We and others found that high CD4 cell counts had a weaker protective effect in South Africa [3,19] than in other regions [5,8–10]. In line with other studies [24,31,32], this indicates that KS diagnosis and treatment will remain a relevant aspect of HIV care in Southern Africa, also

as access to ART is improving. Further research is needed to understand why patients with high current CD4 cell counts still develop KS, especially in Southern Africa but also in other regions of the world [33,34].

Conclusion

Despite ART-related declines in KS incidence, men and women in South Africa and MSM remain at higher risk of developing KS than other HIV-positive persons, probably due to higher HHV-8 coinfection rates. While a vaccine against HHV-8 remains unavailable, early ART initiation and maintaining high CD4 cell counts are essential to reduce KS incidence in populations at high risk for HHV-8 coinfection.

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Table 1: Characteristics of included adults at ART initiation.

	Asia-Pacific N (%)	South Africa N (%)	Latin America N (%)	North America N (%)	Europe N (%)
All adults	2,641 (100%)	21,421 (100%)	8,454 (100%)	16,742 (100%)	158,882 (100%)
Median follow-up time (IQR) [years]	2.7 (1.7-3.9)	2.0 (0.8-4.0)	4.6 (1.9-8.1)	4.2 (1.7-8.5)	4.4 (1.8-8.4)
Gender					
Women	816 (31%)	13,554 (63%)	2,264 (27%)	4,218 (25%)	44,198 (28%)
Men	1825 (69%)	7,867 (37%)	6,190 (73%)	12,524 (75%)	114,684 (72%)
Median age at ART initiation (IQR) [years]	36.3 (30.5- 43.1)	36.4 (31.0-42.7)	35.6 (29.7-42.9)	39.6 (33.8-46.1)	37.3 (31.4-44.5)
Age at ART initiation [years]					
16-25	233 (9%)	1,719 (8%)	993 (12%)	923 (6%)	13,186 (8%)
26-35	1053 (40%)	8,549 (40%)	3,372 (40%)	4,770 (28%)	57,333 (36%)
36-45	871 (33%)	7,689 (36%)	2,568 (30%)	6,825 (41%)	54,749 (34%)
46-55	355 (13%)	2,851 (13%)	1,111 (13%)	3,305 (20%)	23,460 (15%)
≥ 56	129 (5%)	613 (3%)	410 (5%)	919 (5%)	10,154 (6%)
Mode of infection					
MSM	616 (23%)	NR	3,543 (42%)	8,419 (50%)	62,314 (39%)
PWID	164 (6%)	NR	169 (2%)	1,794 (11%)	17,241 (11%)
Heterosexual	1678 (64%)	17,965 (84%)	3,671 (43%)	4,965 (30%)	65,445 (41%)
Other	175 (7%)	9 (<1%)	91 (1%)	258 (2%)	3,520 (2%)
Missing	8 (<1%)	3,447 (16%)	980 (12%)	1,306 (8%)	10,362 (7%)
First line ART regimen					
NNRTI-based	2375 (90%)	20,267 (95%)	6,361 (75%)	6,167 (37%)	66,569 (42%)
PI-based	229 (9%)	1,107 (5%)	1,891 (22%)	9,044 (54%)	80,995 (51%)
Other ART	37 (1%)	47 (<1%)	202 (2%)	1,531 (9%)	11,318 (7%)
Year of ART initiation					
1996-1998	0 (0%)	0 (0%)	107 (1%)	5,332 (32%)	18,771 (12%)
1999-2003	100 (4%)	99 (<1%)	1,926 (23%)	5,167 (31%)	43,004 (27%)
2004-2007	510 (19%)	10,365 (48%)	2,786 (33%)	4,055 (24%)	39,388 (25%)
2008-2014	2,031 (77%)	10,957 (51%)	3,635 (43%)	2,188 (13%)	57,719 (36%)
CDC stage at ART initiation					
A/B	1,225 (46%)	16,561 (77%)	3,850 (46%)	11,920 (71%)	122,365 (77%)
C	921 (35%)	746 (3%)	1,183 (14%)	2,536 (15%)	19,708 (12%)

Missing	495 (19%)	4,114 (19%)	3,421 (40%)	2,286 (14%)	16,809 (11%)
Median CD4 cell count at ART initiation (IQR) [cells/µl]	137 (43-234)	107 (43-176)	165 (61-273)	233 (93-378)	250 (128-369)
CD4 cell count at ART initiation [cells/µl]					
< 50	680 (26%)	5,461 (25%)	1,509 (18%)	2,620 (16%)	17,691 (11%)
50-99	327 (12%)	3,915 (18%)	1,031 (12%)	1,318 (8%)	11,749 (7%)
100-199	604 (23%)	7,178 (34%)	1,649 (20%)	2,620 (16%)	25,890 (16%)
200-349	736 (28%)	2,589 (12%)	2,145 (25%)	4,205 (25%)	48,185 (30%)
350-499	95 (4%)	395 (2%)	584 (7%)	2,340 (14%)	23,895 (15%)
500-699	16 (1%)	188 (1%)	204 (2%)	1,343 (8%)	11,225 (7%)
≥ 700	6 (<1%)	81 (<1%)	81 (1%)	694 (4%)	5,498 (3%)
Missing	177 (7%)	1,614 (8%)	1,251 (15%)	1,602 (10%)	14,749 (9%)
Median HIV RNA at ART initiation (IQR) [log10	5.0 (4.5-5.4)	4.5 (2.7-5.3)	4.9 (4.3-5.4)	4.5 (3.5-5.2)	4.8 (4.1-5.3)
HIV RNA at ART initiation [log10 copies/ml]					
< 2.7	43 (2%)	1,192 (6%)	278 (3%)	2,485 (15%)	13,057 (8%)
2.7-3.9	201 (8%)	589 (3%)	699 (8%)	2,392 (14%)	18,352 (12%)
4.0-4.9	760 (29%)	1,306 (6%)	2,273 (27%)	5,132 (31%)	50,850 (32%)
≥ 5.0	1,044 (40%)	1,633 (8%)	2,673 (32%)	4,499 (27%)	54,417 (34%)
Missing	593 (22%)	16,701 (78%)	2,531 (30%)	2,234 (13%)	22,206 (14%)

ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; KS, Kaposi sarcoma; MSM, men who have sex with men; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NR, not reported; PI, protease-inhibitor; PWID, persons who inject drugs; RNA, ribonucleic acid.

Table 2: Regional risk factors for incident KS in adults who initiated ART.

	South Africa HR* (95% CI)	Latin America HR* (95% CI)	North America HR* (95% CI)	Europe HR* (95% CI)	p-value for interaction**
Gender					<0.001
Male	1.00	1.00	1.00	1.00	
Female	0.61 (0.44 - 0.85)	0.19 (0.09 - 0.41)	0.20 (0.12 - 0.34)	0.29 (0.25 - 0.35)	
Age at ART initiation					0.003
Per decade increase	0.76 (0.62 - 0.93)	0.88 (0.72 - 1.09)	1.17 (1.01 - 1.36)	1.04 (0.99 - 1.09)	

* Adjusted for current CD4 cell count and its interaction with region, gender and its interaction with region, age and its interaction with region, calendar year of ART start, and first-line ART regimen.

** Derived from likelihood ratio test comparing the main adjusted model with the model without interaction of a specific variable with region.

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio, KS, Kaposi sarcoma.

Table 3: Comparison of KS risk between different regions and Europe: Crude and adjusted HRs for developing KS at 2 years after ART initiation in women and men.

	Women		Men	
	Crude HR (95% CI)	**Adjusted HR* (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**
Region				
Europe	1.00	1.00	1.00	1.00
North America	1.16 (0.68 - 2.00)	0.50 (0.24 - 1.04)	1.65 (1.35 - 2.01)	0.75 (0.44 - 1.27)
Latin America	0.73 (0.33 - 1.63)	0.43 (0.14 - 1.27)	1.17 (0.84 - 1.64)	0.65 (0.29 - 1.48)
South Africa	3.19 (2.26 - 4.52)	4.56 (2.73 - 7.62)	1.44 (1.03 - 2.00)	2.21 (1.34 - 3.63)

* For HIV-positive patients with a current CD4 cell count of 350-499 cells/µl who initiated an NNRTI-based regimen between 2008-2014 at the age of 40 years.

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio.

Figure 1: Map of countries contributing patient data to the descriptive analyses.

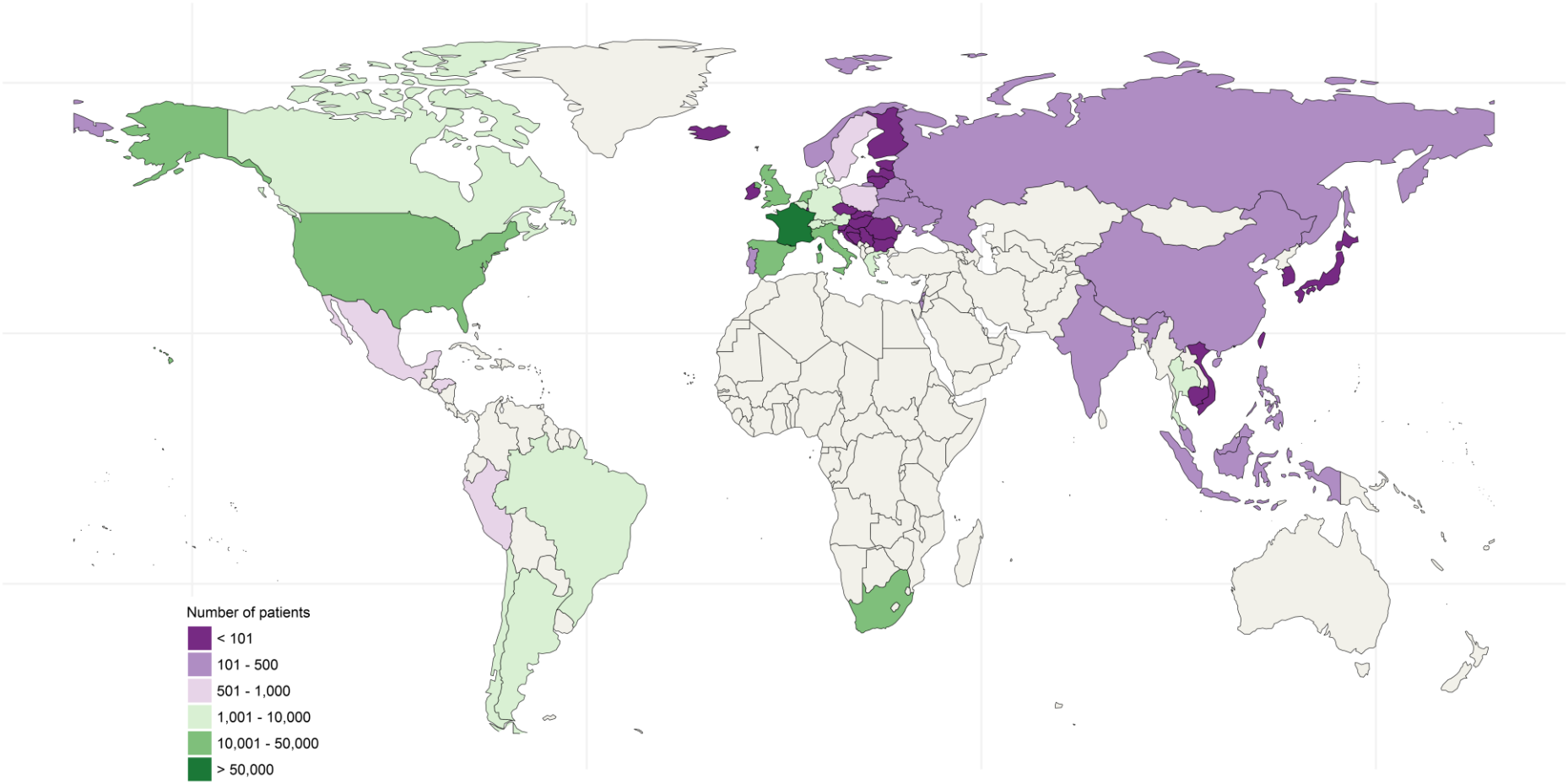
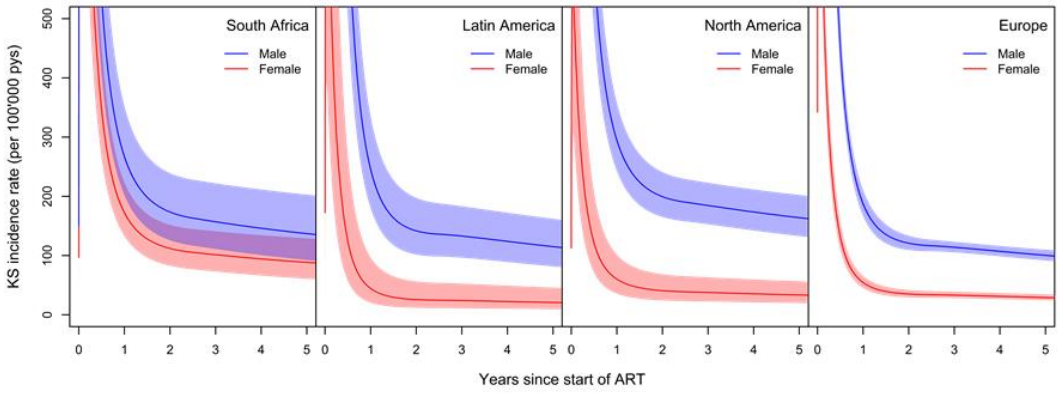
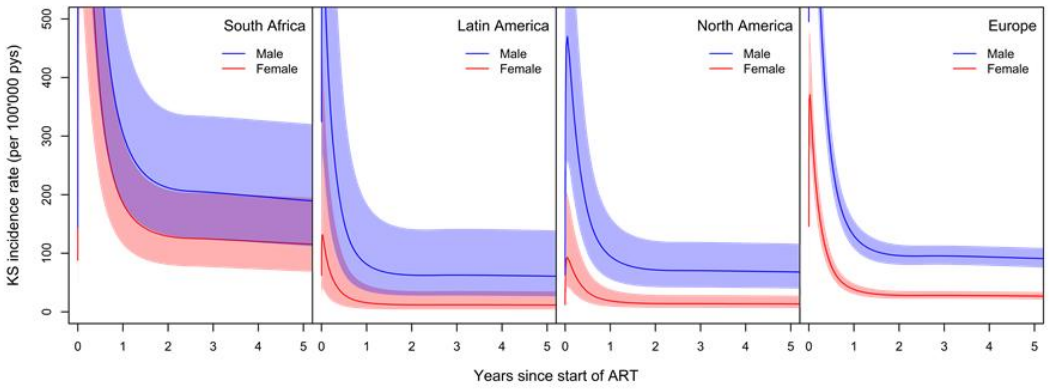


Figure 2: KS incidence rates by time since ART initiation in men and women predicted from the crude model with gender and its interaction with region (Panel A), and predicted from the main adjusted model for men and women with a current CD4 cell count of 350-499 cells/µl who initiated an NNRTI-based first-line ART regimen between 2008-2014 at the age of 40 years (Panel B). ART, antiretroviral therapy; KS, Kaposi sarcoma; NNRTI, non-nucleoside reverse transcriptase inhibitor; pys, person-years.

Panel A

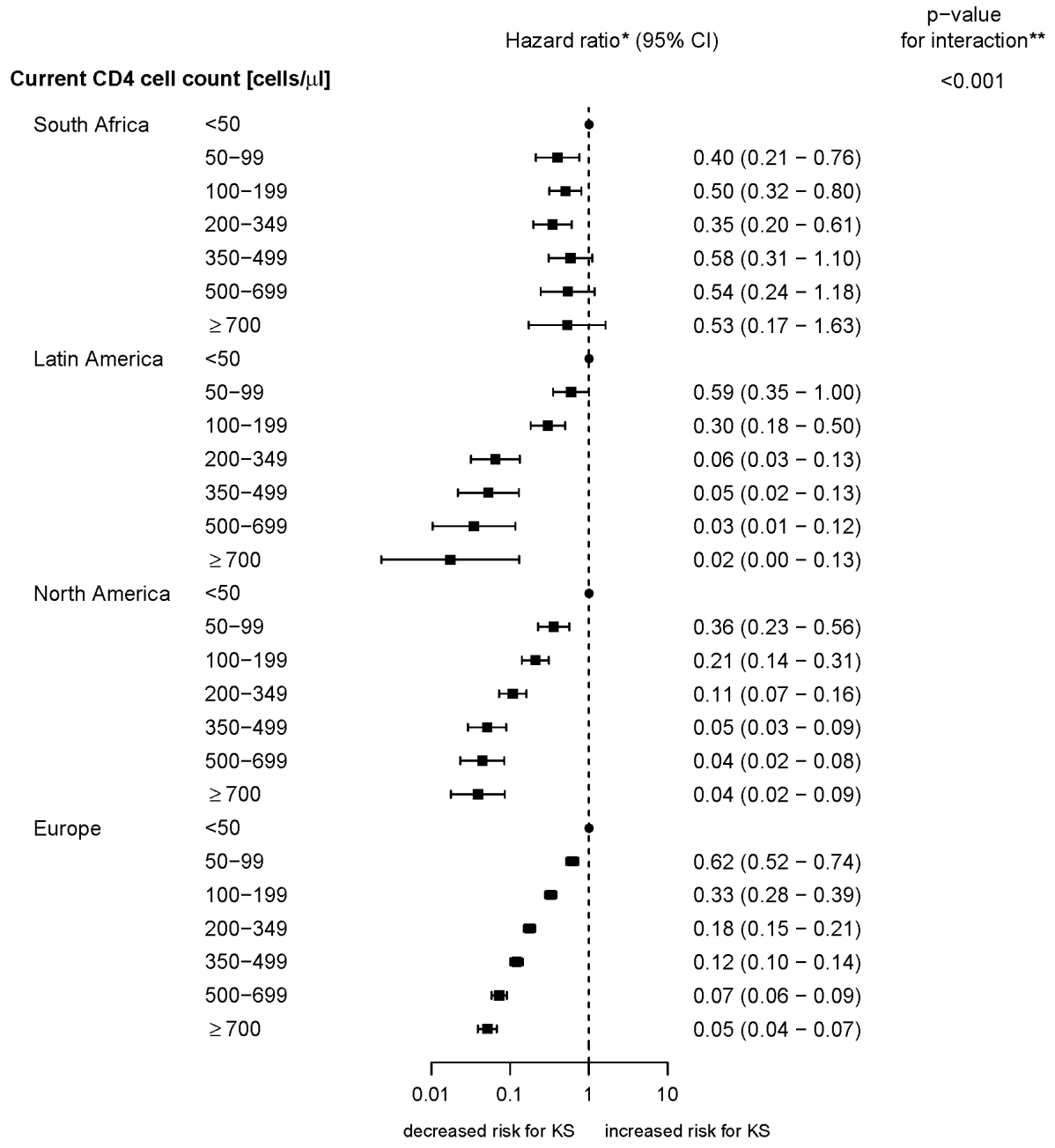


Panel B



ART, antiretroviral therapy; KS, Kaposi sarcoma; NNRTI, non-nucleoside reverse transcriptase inhibitor; pys, person-years.

Figure 3: Regional effects of current CD4 cell counts on the risk of developing Kaposi sarcoma in adults who initiated antiretroviral therapy.



* Adjusted for gender and its interaction with region, age and its interaction with region, calendar year of ART start, and first-line ART regimen.

** Derived from likelihood ratio test comparing the main adjusted model with the model without interaction of a specific variable with region.

ART, antiretroviral therapy; CI, confidence interval; KS, Kaposi sarcoma

Comparison of Kaposi sarcoma risk in HIV-positive adults across five continents: a multiregional multicohort study

The AIDS-defining Cancer Project Working Group for IeDEA and COHERE in EuroCoord

Supplementary material

Boxes

- **Supplementary box S1: Collection and merging of cohort data.**

Figures

- **Supplementary figure S1: Identification of study population for analysis.** The flow diagram shows the number of included and excluded patients.
- **Supplementary figure S2:** KS incidence rates by time since ART initiation in men and women predicted from the crude model with gender and its interaction with region.
- **Supplementary figure S3:** KS incidence rates by time since ART initiation in MSM, heterosexual men and women predicted from the crude model with exposure group.
- **Supplementary figure S4:** KS incidence rates by time since ART initiation in MSM, heterosexual men, and women predicted from the crude model with exposure group (Panel A), and predicted from the main adjusted model for MSM, heterosexual men, and women with a current CD4 cell count of 350-499 cells/µl who initiated an NNRTI-based first-line ART regimen between 2008-2014 at the age of 40 years (Panel B). ART, antiretroviral therapy; KS, Kaposi sarcoma; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; pys, person-years.

Tables

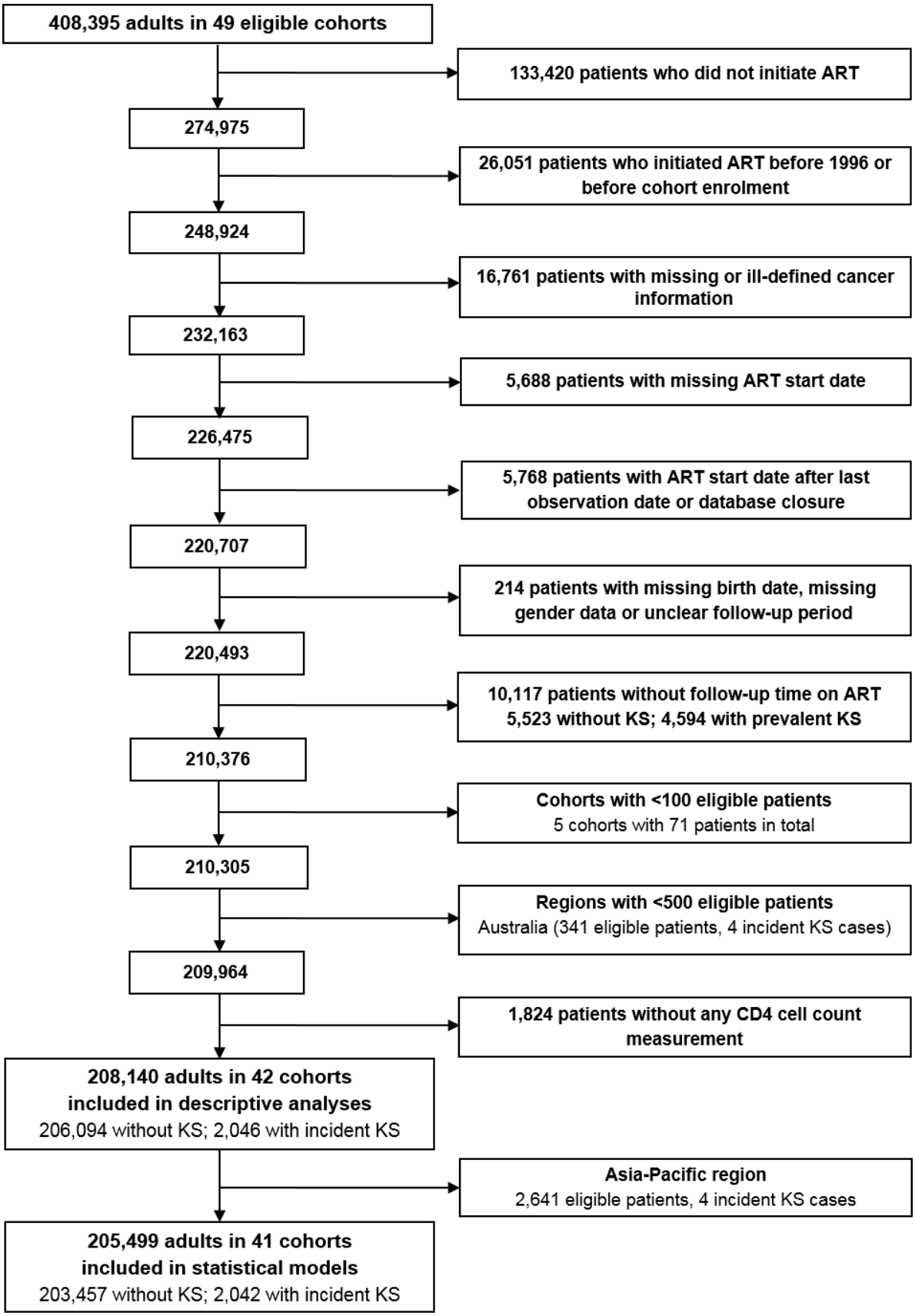
- **Supplementary table S1:** Characteristics of adults with incident KS.
- **Supplementary table S2:** Raw overall KS incidence rates per 100,000 pys by region.

- **Supplementary table S3:** Raw KS incidence rates per 100,000 pys and 95% CIs stratified by region and current CD4 cell count. With only four KS cases in the Asia-Pacific region, data are not shown.
- **Supplementary table S4:** Raw KS incidence rates per 100,000 pys and 95% CIs stratified by region and risk factor.
- **Supplementary table S5:** Effect of calendar year of ART start and first-line ART regimen on the risk of developing KS.
- **Supplementary table S6:** KS incidence rates per 100,000 pys and 95% CIs at 2 years after ART initiation predicted for patients with a current CD4 cell count of 350-499 cells/µl who initiated an NNRTI-based regimen between 2008-2014 at the age of 40 years from the adjusted models with gender (upper two rows) or exposure group (lower two rows).
- **Supplementary table S7:** Raw overall KS incidence rates per 100,000 pys by region excluding the first three months after ART initiation in a sensitivity analysis.
- **Supplementary table S8:** Comparison of KS risk between different regions and Europe, crude and adjusted HRs for being diagnosed with KS at 2 years after ART initiation in women and men from a sensitivity analysis excluding the first three months on ART.
- **Supplementary table S9:** Regional risk factors for incident KS in adults who initiated ART, from a sensitivity analysis excluding the first three months after ART initiation.
- **Supplementary table S10:** KS incidence rates per 100,000 pys and 95% CIs at 2 years after ART initiation from a sensitivity analysis excluding the first three months on ART; predicted for patients with a current CD4 cell count of 350-499 cells/µl who initiated an NNRTI-based regimen between 2008-2014 at the age of 40 years from the adjusted models with gender (upper two rows) or exposure group (lower two rows).

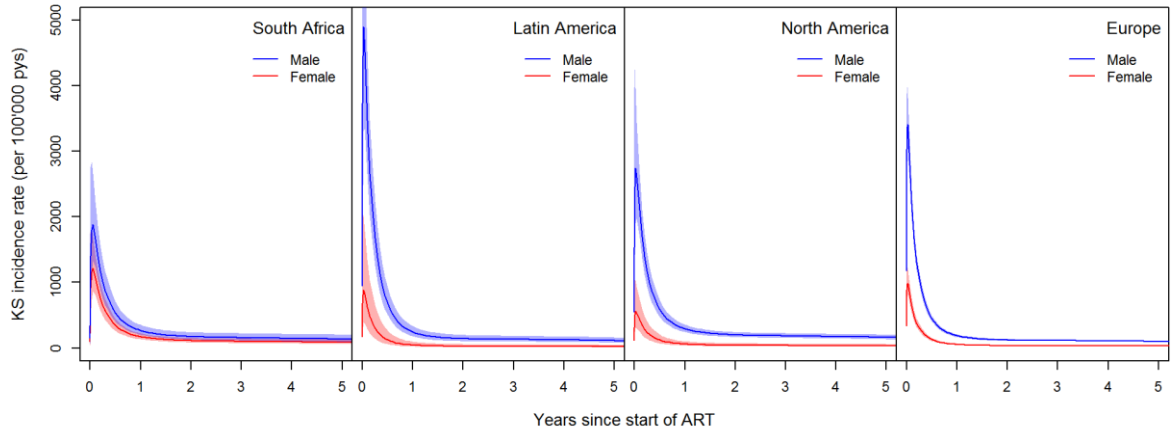
Supplementary box S1: Collection and merging of cohort data.

We analyzed longitudinal routine clinical care data of HIV-positive patients within the framework of the International epidemiology Databases to Evaluate AIDS (IeDEA) and the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. COHERE in EuroCoord contributed data from 24 cohorts covering 36 countries through the 2014 merger. Cohorts participating in IeDEA and COHERE in EuroCoord routinely collect clinical, demographic, laboratory, and treatment data during enrollment and follow-up visits. Patient data are then de-identified and transferred to regional data centres for merging. Through standard procedures for data request we obtained regional data sets in their respective standard data exchange formats from the data centers in 2014. We performed quality checks, harmonized the regional data sets by renaming variables and creating new variables based on available information, and eventually combined them into one multiregional data set for use in this analysis.

Supplementary figure S1: Identification of study population for analysis. The flow diagram shows the number of included and excluded patients.

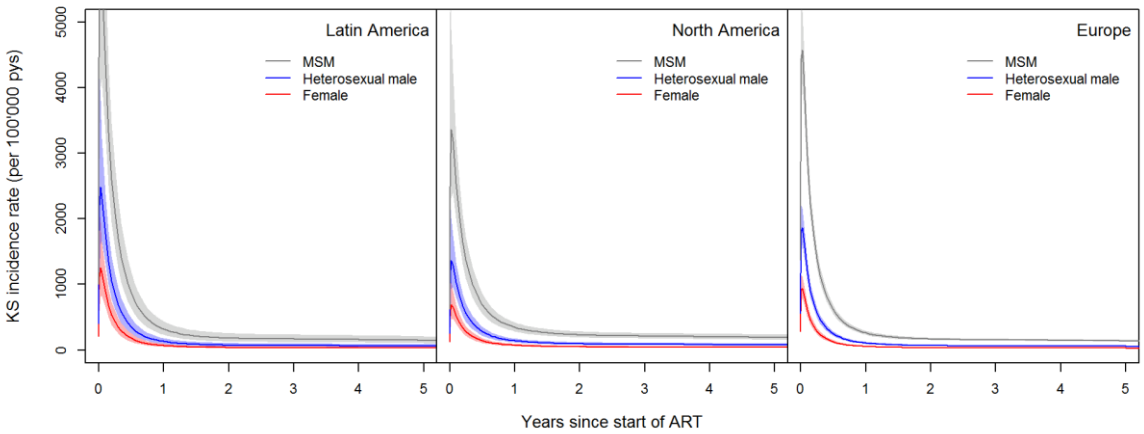


Supplementary figure S2: KS incidence rates by time since ART initiation in men and women predicted from the crude model with gender and its interaction with region.



ART, antiretroviral therapy; KS, Kaposi sarcoma; pys, person-years.

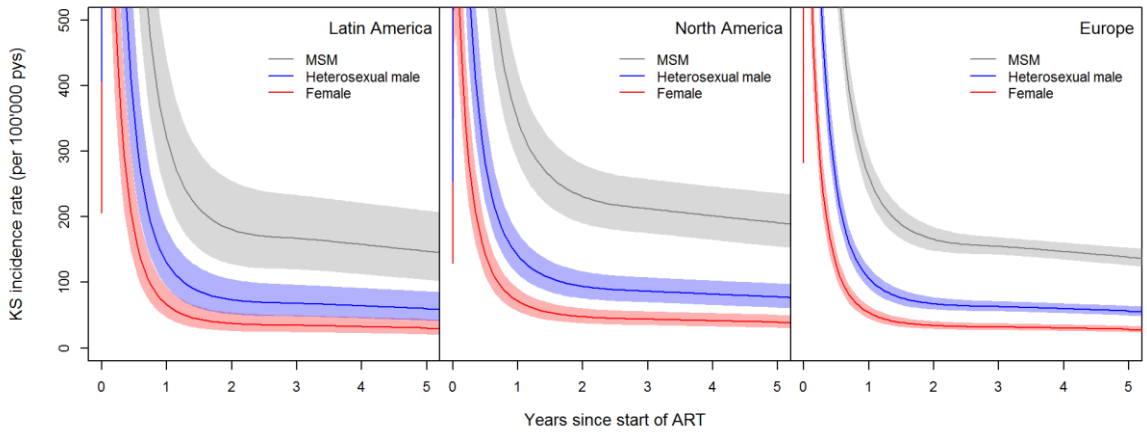
Supplementary figure S3: KS incidence rates by time since ART initiation in MSM, heterosexual men and women predicted from the crude model with exposure group.



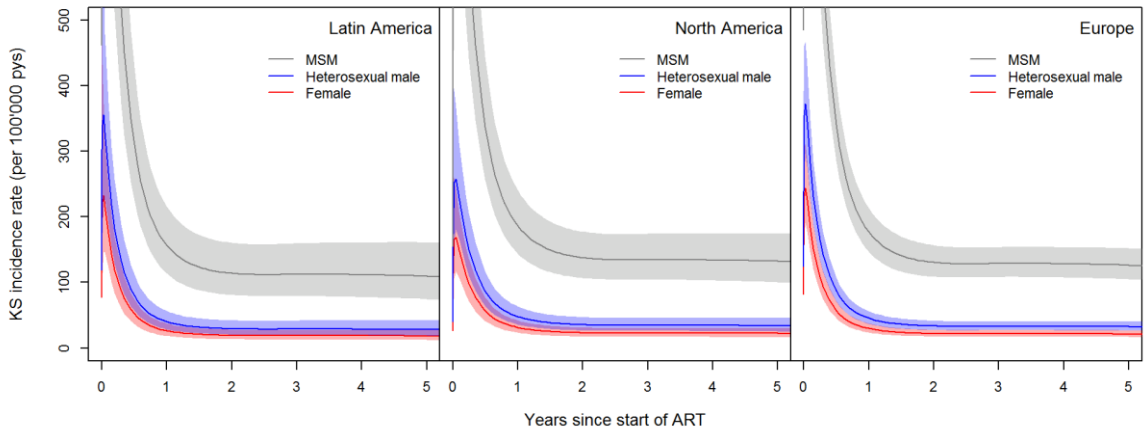
ART, antiretroviral therapy; KS, Kaposi sarcoma; MSM, men who have sex with men; pys, person-years.

Supplementary Figure S4: KS incidence rates by time since ART initiation in MSM, heterosexual men, and women predicted from the crude model with exposure group (Panel A), and predicted from the main adjusted model for MSM, heterosexual men, and women with a current CD4 cell count of 350-499 cells/µl who initiated an NNRTI-based first-line ART regimen between 2008-2014 at the age of 40 years (Panel B). ART, antiretroviral therapy; KS, Kaposi sarcoma; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; pys, person-years.

Panel A



Panel B



ART, antiretroviral therapy; KS, Kaposi sarcoma; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; py, person-years.

Supplementary table S1: Characteristics of adults with incident KS. With only four incident KS cases, data for the Asia-Pacific region are not shown.

	South Africa N (%)	Latin America N (%)	North America N (%)	Europe N (%)
All KS cases	150 (100%)	109 (100%)	211 (100%)	1572 (100%)
Median time to KS diagnosis (IQR) [years]	0.4 (0.2-1.4)	0.3 (0.1-1.3)	0.8 (0.2-3.8)	0.5 (0.1-2.6)
Gender				
Women	81 (54%)	7 (6%)	15 (7%)	160 (10%)
Men	69 (46%)	102 (94%)	196 (93%)	1412 (90%)
Median age at KS diagnosis (IQR) [years]	36.0 (30.2-40.9)	36.7 (31.4-41.7)	42.9 (37.6-48.7)	40.2 (34.1-47.8)
Mode of infection				
MSM	NR	71 (65%)	158 (75%)	1037 (66%)
PWID	NR	0 (0%)	7 (3%)	61 (4%)
Heterosexual	130 (87%)	26 (24%)	31 (15%)	367 (23%)
Other	0 (0%)	1 (1%)	3 (1%)	20 (1%)
Missing	20 (13%)	11 (10%)	12 (6%)	87 (6%)
First line ART regimen				
NNRTI-based	144 (96%)	76 (70%)	61 (29%)	532 (34%)
PI-based	6 (4%)	31 (28%)	129 (61%)	934 (59%)
Other ART	0 (0%)	2 (2%)	21 (10%)	106 (7%)
Year of ART initiation				
1996-1998	0 (0%)	2 (2%)	85 (40%)	336 (21%)
1999-2003	0 (0%)	30 (28%)	71 (34%)	548 (35%)
2004-2007	88 (59%)	31 (28%)	42 (20%)	344 (22%)
2008-2014	62 (41%)	46 (42%)	13 (6%)	344 (22%)
CDC stage at ART initiation				
A/B	107 (71%)	33 (30%)	130 (62%)	1103 (70%)
C	5 (3%)	36 (33%)	59 (28%)	418 (27%)
Missing	38 (25%)	40 (37%)	22 (10%)	51 (3%)
Median CD4 cell count at KS diagnosis (IQR) [cells/µl]	180 (50-320)	77 (29-139)	87 (20-282)	180 (60-348)

CD4 cell count at KS diagnosis [cells/µl]				
< 50	33 (22%)	32 (29%)	73 (35%)	292 (19%)
50-99	12 (8%)	19 (17%)	23 (11%)	179 (11%)
100-199	33 (22%)	25 (23%)	30 (14%)	256 (16%)
200-349	23 (15%)	8 (7%)	30 (14%)	301 (19%)
350-499	21 (14%)	6 (6%)	14 (7%)	189 (12%)
500-699	8 (5%)	1 (1%)	10 (5%)	103 (7%)
≥ 700	4 (3%)	0 (0%)	6 (3%)	49 (3%)
Missing	16 (11%)	18 (17%)	25 (12%)	203 (13%)
Median HIV RNA at KS diagnosis (IQR) [log10 copies/ml]	1.7 (1.7-2.2)	4.4 (1.9-5.0)	3.8 (2.3-5.1)	3.4 (2.0-5.2)
HIV RNA at KS diagnosis [log10 copies/ml]				
< 2.7	63 (42%)	25 (23%)	70 (33%)	503 (32%)
2.7-3.9	4 (3%)	9 (8%)	25 (12%)	189 (12%)
4.0-4.9	5 (3%)	23 (21%)	30 (14%)	182 (12%)
≥ 5.0	4 (3%)	20 (18%)	51 (24%)	385 (24%)
Missing	74 (49%)	32 (29%)	35 (17%)	313 (20%)

ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; KS, Kaposi sarcoma; MSM, men who have sex with men; NNRTI, non-nucleoside reverse-transcriptase inhibitors; NR, not reported; PI, protease-inhibitors; PWID, persons who inject drugs; RNA, ribonucleic acid.

Supplementary table S2: Raw overall KS incidence rates per 100,000 pys by region.

	Patients (N)	Person-years	Cases (N)	Incidence rate (95% CI)
Region				
Asia-Pacific	2,641	7,757	4	52 (19-137)
South Africa	21,421	53,648	150	280 (238-328)
Latin America	8,454	44,603	109	244 (203-295)
North America	16,742	88,952	211	237 (207-271)
Europe	158,882	871,612	1,572	180 (172-190)

CI, confidence interval; KS, Kaposi sarcoma; N, number; pys, person-years.

Supplementary table S3: Raw KS incidence rates per 100,000 pys and 95% CIs, stratified by region and current CD4 cell count. With only four incident KS cases, data for the Asia-Pacific region are not shown.

	South Africa			Latin America			North America			Europe		
	pys	Cases (N)	Incidence rate (95% CI)	pys	Cases (N)	Incidence rate (95% CI)	pys	Cases (N)	Incidence rate (95% CI)	pys	Cases (N)	Incidence rate (95% CI)
Current CD4 cell count [cells/µl]												
< 50	2,631	36	1368 (987 - 1897)	1,356	40	2950 (2164 - 4022)	4,002	81	2024 (1628 - 2516)	14,272	320	2242 (2010 - 2502)
50-99	3,183	13	408 (237 - 703)	1,607	22	1369 (901 - 2079)	3,439	24	698 (468 - 1041)	18,257	195	1068 (928 - 1229)
100-199	10,373	39	376 (275 - 515)	5,258	27	514 (352 - 749)	9,765	37	379 (275 - 523)	64,653	290	449 (400 - 503)
200-349	15,975	25	156 (106 - 232)	10,898	10	92 (49 - 171)	20,021	36	180 (130 - 249)	167,460	345	206 (185 - 229)
350-499	11,299	22	195 (128 - 296)	10,111	6	59 (27 - 132)	19,529	15	77 (46 - 127)	204,687	232	113 (100 - 129)
500-699	6,955	11	158 (88 - 286)	8,603	3	35 (11 - 108)	17,834	11	62 (34 - 111)	209,193	122	58 (49 - 70)
≥ 700	2,778	4	144 (54 - 384)	6,127	1	16 (2 - 116)	14,296	7	49 (23 - 103)	183,050	68	37 (29 - 47)

ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; KS, Kaposi sarcoma; MSM, men who have sex with men; NNRTI, non-nucleoside reverse-transcriptase inhibitors; PI, protease-inhibitors; pys, person-years.

Supplementary table S4: Raw KS incidence rates per 100,000 pys and 95% CIs, stratified by region and risk factor. With only four incident KS cases, data for the Asia-Pacific region are not shown.

	South Africa	Latin America	North America	Europe
Gender and sexual orientation				
Women	231 (186-287)	56 (27-117)	58 (35-97)	65 (55-76)
Men	371 (293-470)	318 (262-387)	310 (269-356)	226 (215-238)
Heterosexual men	-	216 (142-328)	167 (114-243)	119 (107-133)
MSM	-	388 (307-489)	361 (309-422)	311 (292-330)
Age at ART initiation [years]				
16-25	303 (176-523)	248 (141-438)	95 (36-253)	115 (93-143)
26-35	323 (257-406)	268 (202-355)	220 (170-285)	167 (154-181)
36-45	255 (192-338)	256 (185-355)	247 (202-302)	177 (163-193)
46-55	209 (124-353)	138 (69-276)	278 (208-373)	236 (210-266)
≥ 56	162 (40-646)	251 (104-602)	241 (130-449)	254 (213-304)
First line ART regimen				
NNRTI-based	288 (244-339)	231 (185-290)	232 (180-298)	159 (146-173)
PI-based	176 (79-393)	293 (206-417)	236 (198-280)	199 (186-212)
Other ART	-	168 (42-672)	268 (175-411)	160 (132-193)
Year of ART initiation				
1996-1998	-	155 (39-619)	196 (159-243)	173 (156-193)
1999-2003	-	178 (125-255)	235 (186-296)	157 (144-170)
2004-2007	233 (189-287)	176 (124-250)	321 (237-434)	168 (151-187)
2008-2014	404 (315-518)	521 (390-695)	549 (319-946)	279 (251-311)
CDC stage at ART initiation				
A/B	249 (206-301)	168 (119-236)	203 (171-241)	169 (159-179)
C	332 (138-797)	522 (376-723)	470 (364-607)	356 (323-392)
Missing	-	-	-	-

ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; KS, Kaposi sarcoma; MSM, men who have sex with men; NNRTI, non-nucleoside reverse-transcriptase inhibitors; PI, protease-inhibitors; pys, person-years.

Supplementary table S5: Effect of calendar period of ART initiation and first-line ART regimen on the risk of developing KS.

	Crude HR (95% CI)	Adjusted HR* (95% CI)	p-value for interaction**
Calendar period of ART initiation			0.046
2008-2014	1.00	1.00	
2004-2007	1.04 (0.92 - 1.18)	0.87 (0.76 - 0.99)	
1999-2003	1.30 (1.15 - 1.48)	0.94 (0.83 - 1.07)	
1996-1998	1.60 (1.39 - 1.85)	1.03 (0.89 - 1.20)	
First-line ART regimen			0.71
NNRTI-based	1.00	1.00	
PI-based	1.34 (1.22 - 1.47)	1.12 (1.01 - 1.24)	
Other ART	1.12 (0.92 - 1.35)	1.10 (0.91 - 1.33)	

* Adjusted for calendar year of ART start, first-line ART regimen, current CD4 cell count and its interaction with region, gender and its interaction with region, and age and its interaction with region.

** Derived from likelihood ratio test comparing the main adjusted model with the model without interaction of a specific variable with region.

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratios; KS, Kaposi sarcoma; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Supplementary table S6: KS incidence rates per 100,000 pys and 95% CIs at 2 years after ART initiation predicted for patients with a current CD4 cell count of 350-499 cells/µl who initiated an NNRTI-based regimen between 2008-2014 at the age of 40 years from the adjusted models with gender (upper two rows) or exposure group (lower two rows).

	South Africa	**Latin America**	**North America**	**Europe**
	IR (95% CI)*	**IR (95% CI)***	**IR (95% CI)***	**IR (95% CI)***
Gender and exposure group				
Women	129 (80-208)	12 (4-36)	14 (7-29)	28 (22-36)
Men	212 (131-344)	63 (28-142)	72 (42-121)	96 (80-115)
Heterosexual men	-	29 (20-42)	35 (27-47)	34 (27-41)
MSM	-	114 (81-160)	138 (107-178)	131 (109-157)

*Incidence rate (IR) per 100,000 person-years and 95% confidence intervals (CI)

Supplementary table S7: Raw overall KS incidence rates per 100,000 pys by region, excluding the first three months after ART initiation in a sensitivity analysis.

	Patients (N)	Person-years	Cases (N)	Incidence rate (95% CI)
Region				
Asia-Pacific	2,505	7,115	3	39 (13 - 120)
South Africa	19,050	48,608	94	176 (144 - 216)
Latin America	8,075	42,536	61	137 (107 - 176)
North America	16,253	84,812	143	161 (137 – 190)
Europe	151,742	832,736	945	109 (102 - 116)

CI, confidence interval; KS, Kaposi sarcoma; N, number; pys, person-years.

Supplementary table S8: Comparison of KS risk between different regions and Europe, crude and adjusted HRs for being diagnosed with KS at 2 years after ART initiation in women and men from a sensitivity analysis excluding the first three months after ART initiation.

	Women		Men	
	Crude HR (95% CI)	**Adjusted HR* (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR* (95% CI)**
Region				
Europe	1.00	1.00	1.00	1.00
North America	1.09 (0.60 - 1.98)	0.56 (0.26 - 1.23)	1.58 (1.29 - 1.93)	0.90 (0.52 - 1.54)
Latin America	0.47 (0.15 - 1.50)	0.25 (0.06 - 1.05)	1.18 (0.86 - 1.62)	0.62 (0.25 - 1.54)
South Africa	2.51 (1.70 - 3.70)	3.92 (2.23 - 6.88)	1.50 (1.05 - 2.15)	2.61 (1.53 - 4.45)

* Predictions for HIV-positive patients with a current CD4 cell count of 350-499 cells/µl who initiated an NNRTI-based regimen between 2008-2014 at the age of 40 years.

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio.

Supplementary table S9: Regional risk factors for incident KS in adults who initiated ART from a sensitivity analysis excluding the first three months after ART initiation.

	South Africa HR* (95% CI)	Latin America HR* (95% CI)	North America HR* (95% CI)	Europe HR* (95% CI)
Gender				
Male	1.00	1.00	1.00	1.00
Female	0.51 (0.34 - 0.78)	0.14 (0.04 - 0.44)	0.21 (0.12 - 0.39)	0.34 (0.28 - 0.42)
Current CD4 cell count [cells/µl]				
< 50	1.00	1.00	1.00	1.00
50-99	0.26 (0.08 - 0.82)	0.41 (0.19 - 0.88)	0.23 (0.12 - 0.44)	0.42 (0.33 - 0.55)
100-199	0.48 (0.23 - 1.01)	0.23 (0.12 - 0.45)	0.17 (0.11 - 0.28)	0.23 (0.18 - 0.28)
200-349	0.32 (0.14 - 0.69)	0.04 (0.02 - 0.11)	0.10 (0.06 - 0.15)	0.13 (0.11 - 0.16)
350-499	0.61 (0.27 - 1.37)	0.04 (0.01 - 0.11)	0.06 (0.03 - 0.10)	0.09 (0.07 - 0.11)
500-699	0.63 (0.25 - 1.62)	0.03 (0.01 - 0.10)	0.03 (0.02 - 0.07)	0.05 (0.04 - 0.07)
≥ 700	0.68 (0.20 - 2.36)	-	0.04 (0.02 - 0.09)	0.04 (0.03 - 0.05)
Age at ART initiation				
Per decade increase	0.79 (0.61 - 1.02)	0.76 (0.57 - 1.02)	1.11 (0.92 - 1.35)	1.01 (0.95 - 1.08)

* Adjusted for current CD4 cell count and its interaction with region, gender and its interaction with region, age and its interaction with region, calendar year of ART start, and first-line ART regimen.

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio, KS, Kaposi sarcoma.

Supplementary table S10: KS incidence rates per 100,000 pys and 95% CIs at 2 years after ART initiation from a sensitivity analysis excluding the first three months on ART; predicted for patients with a current CD4 cell count of 350-499 cells/µl who initiated an NNRTI-based regimen between 2008-2014 at the age of 40 years from the adjusted models with gender (upper two rows) or exposure group (lower two rows).

	South Africa	Latin America	North America	Europe
	IR (95% CI)*	**IR (95% CI)***	**IR (95% CI)***	**IR (95% CI)***
Gender and exposure group				
Women	118 (69-199)	7 (2-31)	17 (8-36)	30 (23-40)
Men	229 (136-387)	55 (22-135)	79 (46-136)	88 (70-110)
Heterosexual men	-	30 (20-44)	33 (23-45)	36 (27-46)
MSM	-	105 (73-151)	115 (85-155)	126 (100-158)

*Incidence rate (IR) per 100,000 person-years and 95% confidence intervals (CI)

ART, antiretroviral therapy; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor.