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# Comparison of Kaposi Sarcoma Risk in Human Immunodeficiency Virus-Positive Adults Across 5 Continents: A Multiregional Multicohort Study

The AIDS-defining Cancer Project Working Group for IeDEA and COHERE in EuroCoord<sup>a</sup>

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

**Methods.** We included cohort data of human immunodeficiency virus (HIV)-positive adults who started ART after 1995 within the framework of 2 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 a period of 1 066 572 person-years, 2046 KS cases were diagnosed. KS incidence rates per 100 000 person-years were 52 in the Asia-Pacific and ranged between 180 and 280 in the other regions. KS risk was 5 times higher in South African women (aHR, 4.56; 95% confidence intervals [CI], 2.73–7.62) than in their European counterparts, and 2 times higher in South African men (2.21; 1.34–3.63). In Europe, Latin, and North America KS risk was 6 times higher in men who have sex with men (aHR, 5.95; 95% CI, 5.09–6.96) than in women. Comparing patients with current CD4 cell counts  $\geq 700$  cells/ $\mu\text{L}$  with those whose counts were  $< 50$  cells/ $\mu\text{L}$ , the KS risk was halved in South Africa (aHR, 0.53; 95% CI, .17–1.63) but reduced by  $\geq 95\%$  in other regions.

**Conclusions.** Despite important ART-related declines in KS incidence, men and women in South Africa and men who have sex with men remain at increased KS risk, likely due to high human herpesvirus 8 coinfection rates. Early ART initiation and maintenance of high CD4 cell counts are essential to further reducing KS incidence worldwide, but additional measures might be needed, especially in Southern Africa.

**Keywords.** Kaposi sarcoma; HIV; antiretroviral therapy; cohort study.

Persons infected with human immunodeficiency virus (HIV) are at high risk of developing Kaposi sarcoma (KS) [1], and this risk seems to vary geographically. KS incidence rates seem to be higher in adults who started 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 healthcare, 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 healthcare varies across regions, and patients in high-income countries start ART at higher CD4 cell counts than those in low- and middle-income settings [11]. We compared KS incidence rates in HIV-positive adults

who started ART across different continents, and we 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 the European Coordinating Committee for the integration of ongoing coordination actions related to clinical and epidemiological HIV research (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 2 geographic 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.

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### 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 (aged  $\geq 16$  years) who started ART after enrollment into the cohort from 1996 onward. We excluded patients without follow-up after ART initiation and patients with no CD4 cell counts during follow-up. We excluded regions with  $< 500$  eligible patients and cohorts with  $< 100$  eligible patients. We excluded the region Asia-Pacific from statistical models owing 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  $\geq 3$  antiretroviral drugs from any class, including protease inhibitors (PIs), nucleoside reverse-transcriptase inhibitors, and nonnucleoside reverse-transcriptase inhibitors (NNRTIs). Patients were assumed to remain on ART once initiated. CD4 cell counts at ART initiation were defined as the measurement nearest ART initiation, within 180 days before to 7 days after initiation. The HIV/AIDS stage at ART initiation was defined according to the US Centers for Disease Control and Prevention [17].

### Statistical Analyses

We calculated raw KS incidence rates by dividing the number of incident KS cases by person-years 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 4 degrees of freedom and allowed for time-dependent region-effects with 2 degrees of freedom. Likelihood ratio tests were used to test for interactions between risk factors and regions. We assessed sex, exposure group (women, heterosexual men, men who have sex with men [MSM]), age at ART initiation (16–25, 26–35, 36–45, 46–55, or  $\geq 56$  years), first-line ART regimen (NNRTI-based, PI-based, other), calendar period of ART initiation (1996–1998, 1999–2003, 2004–2007, or 2008–2014), and current (time-updated) CD4 cell count ( $< 50$ , 50–99, 100–199, 200–349, 350–499, 500–699, or  $\geq 700$  cells/ $\mu\text{L}$ ). Mode of infection, HIV/AIDS stage, and HIV RNA level at ART initiation were assessed in descriptive analyses.

We fit “crude” models with 1 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, sex and its interaction with region, age at ART initiation and its interaction with region, current CD4 cell count and its interaction

with region, first-line ART regimen, and calendar period of ART initiation. The second adjusted model was restricted to the 3 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 3 months of follow-up. KS incidence rates were predicted from adjusted models for patients with a standardized risk factor set: initiation of NNRTI-based regimens between 2008 and 2014 at age 40 years and current CD4 cell count 350–499 cells/ $\mu\text{L}$ . Results are presented as medians with interquartile ranges (IQRs), number and percentage of patients, incidence rates per 100 000 person-years, and hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were performed using Stata 14 (StataCorp) and R (R Foundation) software.

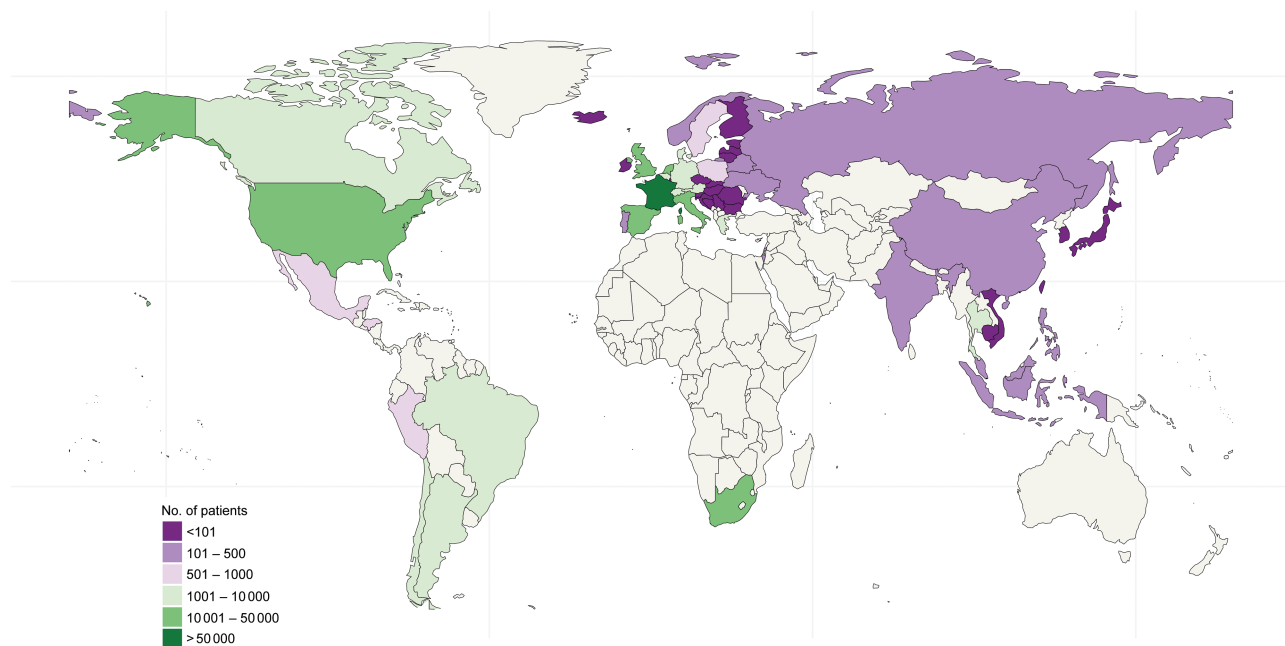
## RESULTS

### Descriptive Analyses

The merged multiregional data set 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 sex (male, 70% vs 69%), risk group (MSM, 33% vs 36%), age (median, 35 years vs 37 years), and CD4 cell count at ART initiation (median, 240 cells/ $\mu\text{L}$  vs 222 cells/ $\mu\text{L}$ ).

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). The median age at ART initiation was 37.3 years (IQR, 31.4–44.4 years) 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%) but not in the Asia-Pacific (34%); data were not available for South Africa. The median CD4 cell count at ART initiation was  $< 200$  cells/ $\mu\text{L}$  in the Asia-Pacific, South Africa, and Latin America and  $> 200$  cells/ $\mu\text{L}$  in North America and Europe (Table 1). In South Africa and the Asia-Pacific,  $< 5\%$  of patients started ART before 2004, but 39% in Europe and 63% in North America started ART between 1996 and 2003. Approximately half of North American and European patients started PI-based regimens, compared with just 22% in Latin America, and  $< 10\%$  in South Africa and the Asia-Pacific. The 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 the course of 1 066 572 person-years, 2046 KS cases were diagnosed (1572 in Europe, 211 in North America, 150 in South Africa, 109 in Latin America, and 4 in the Asia-Pacific; Supplementary Table S1). The median time between ART initiation and KS diagnosis was 0.5 year (IQR, 0.1–2.5



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

years). The median age at KS diagnosis ranged from 35 years in the Asia-Pacific to 43 years in North America. The median CD4 cell count at KS diagnosis was <100 cells/ $\mu$ L in the Asia-Pacific, Latin, and North America and 180 cells/ $\mu$ L in South Africa and Europe.

The raw KS incidence rate per 100 000 person-years was highest in South Africa (280; 95% CI, 238–328), followed by Latin America (244; 203–295), North America (237; 207–271), Europe (180; 172–190), and the Asia-Pacific (52; 19–137; Supplementary Table S2). The raw KS incidence rates were especially high in patients with current CD4 cell counts <50 cells/ $\mu$ L (ranging from 1368 in South Africa to 2950 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 Kaposi Sarcoma

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 sex, 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 sex difference was less pronounced in South Africa ( $P$  for interaction < .001; Table 2 and 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 adjustment for current CD4 cell 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 6 times higher in MSM (aHR 5.95; 5.09–6.96). There was no evidence that the effect of exposure group on KS risk differed across regions ( $P$  for interaction = .19).

In all regions, KS risk was highest in persons with current CD4 cell counts <50 cells/ $\mu$ L. However, comparing patients with current CD4 cell counts  $\geq$ 700 cells/ $\mu$ L to those with cell counts <50 cells/ $\mu$ L, KS risk was halved in South Africa (aHR, 0.53; 95% CI, .17–1.63), but reduced by  $\geq$ 95% in the other regions ( $P$  for interaction < .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 ( $P$  for interaction = .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 those who received NNRTI-based regimens (aHR, 1.12; 95% CI, 1.01–1.24).

#### Comparison of Kaposi Sarcoma Risk Between Regions

In women, KS risk at 2 years after ART initiation was >3 times higher in South Africa than in Europe in crude analyses (HR, 3.19; 95% CI, 2.26–4.52) and almost 5 times higher in analyses adjusted for current CD4 cell count, age at ART initiation, first-line regimen, and calendar period of ART initiation (aHR 4.56; 2.73–7.62; Table 3). The adjusted KS risk tended to be lower in North and Latin American women than in European women,

**Table 1. Characteristics of Included Adults at Antiretroviral Therapy Initiation**

Characteristic	Patients, No. (%) <sup>a</sup>				
	Asia-Pacific (n = 2641)	South Africa (n = 21 421)	Latin America (n = 8454)	North America (n = 16 742)	Europe (n = 158 882)
Follow-up time, median (IQR), y	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)
Sex					
Female	816 (31)	13 554 (63)	2 264 (27)	4 218 (25)	44 198 (28)
Male	1 825 (69)	7 867 (37)	6 190 (73)	12 524 (75)	114 684 (72)
Age at ART initiation, median (IQR), y	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, y					
16–25	233 (9)	1 719 (8)	993 (12)	923 (6)	13 186 (8)
26–35	1 053 (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	1 678 (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	2 375 (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)
CD4 cell count at ART initiation, median (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)
HIV RNA at ART initiation, median (IQR), log <sub>10</sub> copies/mL	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, log <sub>10</sub> 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)	16 333 (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)

Abbreviations: ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NR, not reported; PI, protease inhibitor; PWID, persons who inject drugs.

<sup>a</sup>Data represent No. (%) of patients unless otherwise specified.

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 (1.44; 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 (1.34–3.63) in South Africa. Both changes



**Table 2. Regional Risk Factors for Incident Kaposi Sarcoma in Adults Who Started ART**

Risk Factor	HR (95% CI) <sup>a</sup>				P Value for Interaction <sup>b</sup>
	South Africa	Latin America	North America	Europe	
Sex					
Male	1.00	1.00	1.00	1.00	<.001
Female	0.61 (.44–.85)	0.19 (.09–.41)	0.20 (.12–.34)	0.29 (.25–.35)	
Age at ART initiation (per decade increase)	0.76 (.62–.93)	0.88 (.72–1.09)	1.17 (1.01–1.36)	1.04 (.99–1.09)	.003

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

<sup>a</sup>HRs adjusted for current CD4 cell count and its interaction with region, sex and its interaction with region, age and its interaction with region, calendar year of ART initiation, and first-line ART regimen.

<sup>b</sup>P values derived from likelihood ratio test comparing the main adjusted model with the model without interaction of a specific variable with region.

were mainly due to adjustment for current CD4 cell 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 person-years at 2 years after ART initiation for patients with current CD4 cell counts of 350–499 cells/ $\mu$ L who started NNRTI-based regimens between 2008 and 2014 at age 40 years. Predicted KS incidence rates in women were 12 (95% CI, 4–36) in Latin America, 14 (7–29) in North America, and 28 (22–36) in Europe. In heterosexual men, KS incidence rates were 29 (95% CI, 20–42) in Latin America, 35 (27–47) in North America, and 34 (27–41) in Europe. In South Africa, KS incidence rates remained at 212 (95% CI, 131–344) in men and 129 (80–208) in women.

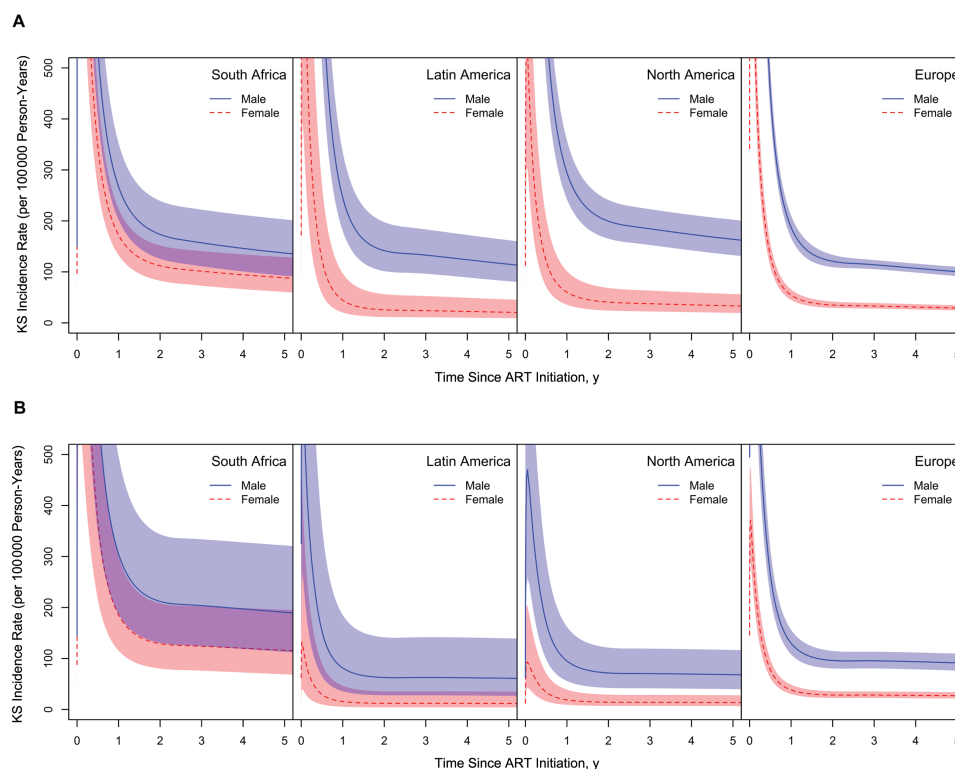
Predicted KS incidence rates in MSM were 114 (95% CI, 81–160) in Latin America, 131 (109–157) in Europe, and 138 (107–178) in North America (Supplementary Table S6).

### Sensitivity Analysis

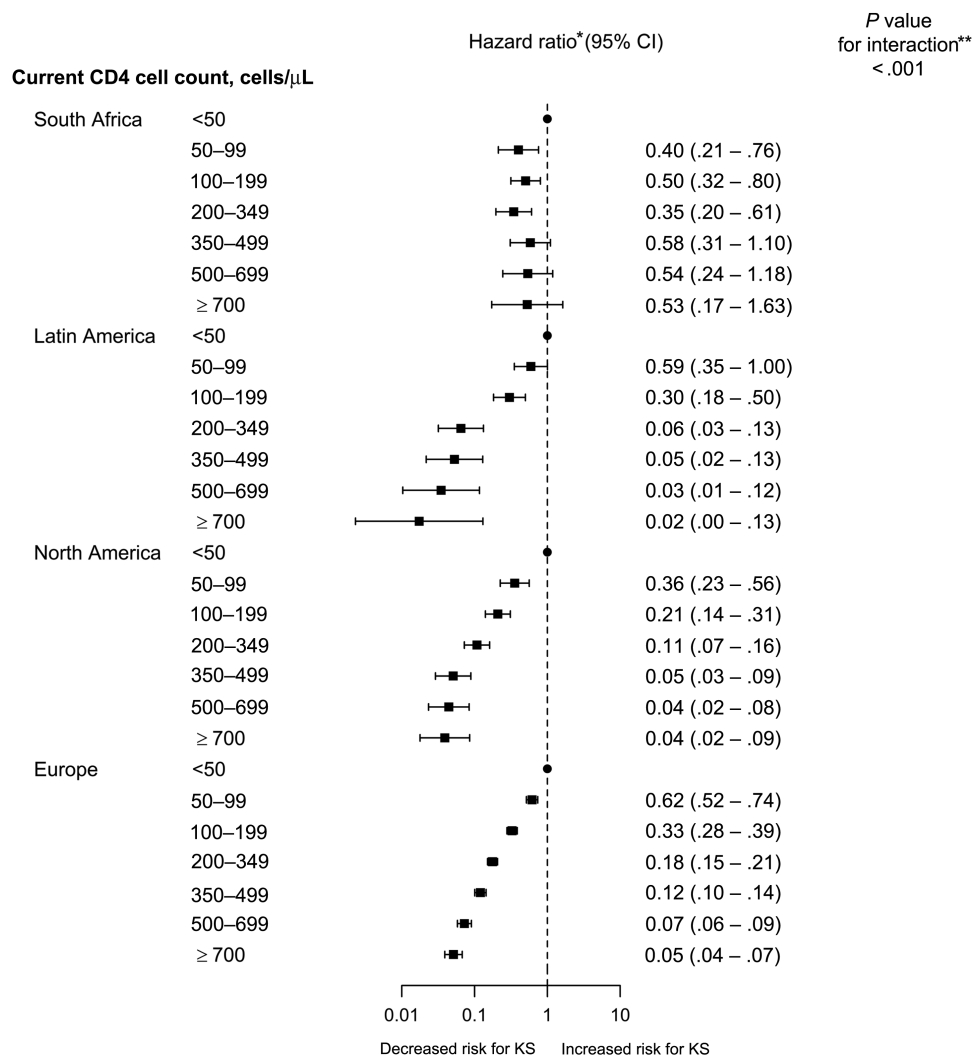
Excluding the first 3 months of follow-up resulted in lower raw KS incidence rates (Supplementary Table S7); other results remained similar (Supplementary Tables S8–S10).

### DISCUSSION

After adjustment for HIV-related risk factors, HIV-positive men and women in South Africa had a higher risk of developing KS



**Figure 2.** Kaposi sarcoma (KS) incidence rates by time since antiretroviral therapy (ART) initiation in men and women predicted from the crude model with sex and its interaction with region (A), and predicted from the main adjusted model for men and women with a current CD4 cell count of 350–499 cells/ $\mu$ L who started a nonnucleoside reverse-transcriptase inhibitor–based first-line ART regimen between 2008 and 2014 at age 40 years (B).



**Figure 3.** Regional effects of current CD4 cell counts on the risk of Kaposi sarcoma (KS) in adults who started antiretroviral therapy (ART). The blocks and horizontal lines represent hazard ratios and 95% confidence intervals (CIs). Points represent the reference categories. \*Adjusted for sex 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.

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/ $\mu$ L was a

strong risk factor for incident KS. However, the clear trend toward lower KS risk with higher current CD4 cell counts seen in Europe, North, and Latin America was not observed in South Africa.

**Table 3. Comparison of Kaposi Sarcoma Risk Between Different Regions and Europe: Crude and Adjusted HRs for Development of KS 2 Years After Antiretroviral Therapy Initiation in Women and Men**

Region	Women		Men	
	Crude HR (95% CI)	Adjusted HR <sup>a</sup> (95% CI)	Crude HR (95% CI)	Adjusted HR <sup>a</sup> (95% CI)
Europe	1.00	1.00	1.00	1.00
North America	1.16 (.68–2.00)	0.50 (.24–1.04)	1.65 (1.35–2.01)	0.75 (.44–1.27)
Latin America	0.73 (.33–1.63)	0.43 (.14–1.27)	1.17 (.84–1.64)	0.65 (.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)

Abbreviations: CI, confidence interval; HR, hazard ratio; KS, Kaposi sarcoma.

<sup>a</sup>For human immunodeficiency virus–positive patients with a current CD4 cell count of 350–499 cells/ $\mu$ L who started a nonnucleoside reverse-transcriptase inhibitor–based regimen between 2008 and 2014 at age 40 years.

This is the first study to directly compare KS risk across several continents in adults who started 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 underreporting of KS, data from South Africa were restricted to 2 urban cohorts that obtained additional KS data through record linkages with a cancer registry [2]. However, these South African data are not necessarily representative of 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; therefore, KS risk in patients continuously receiving ART might be lower than what we found in our analysis for patients after ART initiation. Most patients from North America started ART before 2004 with NNRTI- or PI-based regimens, whereas almost all patients in South Africa started 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 findings in previous studies [4, 5, 10, 19]. These peaks are partly explained by immunodeficiency that persisted after ART initiation, unmasking IRIS-KS [9, 20], and possible misclassification of some prevalent KS as incident KS. However, when we excluded KS cases occurring within 3 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 receiving 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 with 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 sex 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 sex 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 KS than European men after adjustment for HIV-related factors. Besides differences in HHV-8 prevalence, other factors such as environmental exposures and malaria might play a role [28–30]. However, such cofactors 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 KS than European men, but after adjustment 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 KS still develops in patients with high current CD4 cell counts, especially in Southern Africa but also in other regions of the world [33, 34].

In conclusion, despite ART-related declines in KS incidence, men and women in South Africa and MSM remain at higher risk of KS than other HIV-positive persons, probably owing to higher HHV-8 coinfection rates. While a vaccine against HHV-8 remains unavailable, early ART initiation and maintenance of high CD4 cell counts are essential to reducing the incidence of KS in populations at high risk for HHV-8 coinfection.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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