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Changing Incidence and Risk Factors for Kaposi Sarcoma by Time Since Starting Antiretroviral Therapy: Collaborative Analysis of 21 European Cohort Studies

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Background. Kaposi sarcoma (KS) remains a frequent cancer in human immunodeficiency virus (HIV)–positive patients starting combination antiretroviral therapy (cART). We examined incidence rates and risk factors for developing KS in different periods after starting cART in patients from European observational HIV cohorts.

Methods. We included HIV-positive adults starting cART after 1 January 1996. We analyzed incidence rates and risk factors for developing KS up to 90 and 180 days and 1, 2, 5, and 8 years after cART start and fitted univariable and multivariable Cox regression models.

Results. We included 109 461 patients from 21 prospective clinical cohorts in Europe with 916 incident KS cases. The incidence rate per 100 000 person-years was highest 6 months after starting cART, at 953 (95% confidence interval, 866–1048), declining to 82 (68–100) after 5–8 years. In multivariable analyses adjusted for exposure group, origin, age, type of first-line regimen, and calendar year, low current CD4 cell counts increased the risk of developing KS throughout all observation periods after cART initiation. Lack of viral control was not associated with the hazard of developing KS in the first year after cART initiation, but was over time since starting cART increasingly positively associated ($P < .001$ for interaction).

Conclusion. In patients initiating cART, both incidence and risk factors for KS change with time since starting cART. Whereas soon after starting cART low CD4 cell count is the dominant risk factor, detectable HIV-1 RNA viral load becomes an increasingly important risk factor in patients who started cART several years earlier, independently of immunodeficiency.

Keywords. Kaposi sarcoma; HIV; adults; antiretroviral therapy; risk factors.

Kaposi sarcoma (KS) remains a frequent cancer in human immunodeficiency virus (HIV)–positive patients, including in patients who are receiving combination antiretroviral therapy (cART) [1–4]. Higher detection rates of KS and KS becoming evident in the context of the immune reconstitution inflammatory syndrome (IRIS) may contribute to the increased KS risk shortly after cART initiation [5]. Few studies have examined the incidence rate of KS in HIV-positive patients who started cART some years earlier. An earlier analysis of a large US cohort of HIV-positive patients found that the incidence of KS was very high in the first 6 months after cART initiation (1342/100 000 person-years [py]) but decreased substantially thereafter and stabilized at a rate of about 164/100 000 py >6 months after starting cART [3].

Infection with human herpesvirus 8 (HHV-8) is a necessary cause of KS [6]. HHV-8 seroprevalence is high among men who have sex with men (MSM) and in the general population of some regions of sub-Saharan Africa, including Southern Africa and East Africa [6]. Likewise, high rates of KS incidence among patients having started cART have been found among MSM in Europe [2] and patients in Africa [7–9]. Immunodeficiency, as indicated by low CD4 cell counts, and failure to suppress HIV replication have also been identified as risk factors for developing KS in HIV-positive individuals receiving cART [2, 5, 10–12]. However, it is unclear at present whether these risk factors influence KS development similarly soon and many years after starting cART. In particular, the determinants of KS among patients who started cART several years earlier have not been well defined.

The aim of the present study was to gain a better understanding of the factors that drive the incidence of KS among patients initiating cART. We analyzed data from a large collaboration of European HIV cohort studies, the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord to examine KS incidence rates and risk factors for KS in different time intervals after cART initiation, from 30–90 days to 5–8 years.

MATERIALS AND METHODS

COHERE in EuroCoord

The COHERE in EuroCoord is a collaboration of 40 cohorts of HIV-infected patients across Europe, led by 2 data centers in Bordeaux, France, and Copenhagen, Denmark [13]. Twenty-nine

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cohorts provided data for the current project. Patients are followed up every 3–6 months. Participating cohorts collect and transfer standardized data using the HIV Cohorts Data Exchange Protocol [14]. Data collected include sociodemographic factors, CD4 cell counts, HIV-1 RNA viral load measurements, antiretroviral drugs, AIDS-defining events, and deaths. The data set for this analysis was merged on 4 June 2014 and included 29 cohorts with 306 482 patients. Cohorts adhere to local ethical requirements for observational research [13].

Inclusion Criteria and Definitions

We included HIV-positive adults aged ≥16 years who enrolled and started cART after 1 January 1996, when cART became widely available in most parts of Europe. cART was defined as a regimen of ≥3 drugs from any class, including nucleoside reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). We excluded patients with previous antiretroviral therapy exposure to monotherapy or dual therapy. Patients with ≤30 days of follow-up and prevalent KS cases diagnosed before or during the first 30 days after cART start were excluded from analyses. We also excluded patients with missing information for sex, country or region of birth, and date of birth and cohorts with <100 eligible patients.

We defined baseline CD4 cell count as the measurement closest to the start of cART, with a time window of −90 to +30 days. Baseline HIV-1 RNA viral load was the measurement closest to start cART with a time window of −90 to +7 days. Suppression of HIV-1 replication was defined as an HIV-1 RNA viral load ≤500 copies/mL. Late presenters were defined as CD4 cell count <350/μL or Centers for Disease Control and Prevention stage C at enrollment [15]. First-line regimens were classified as NNRTI based, boosted PI based, unboosted PI based, or other. Sex and exposure groups were defined as MSM, heterosexual men, and heterosexual women. Origin (ie, country or region of birth) was categorized as European, African or other.

Statistical Analysis

Observation started 30 days after initiating cART. We used an intention-to-continue-treatment approach, ignoring subsequent treatment changes and interruptions. We split observation time into 6 periods: 30–90 and 91–180 days, 181 days to 12 months, and 1–2, 2–5, and 5–8 years. The same patient could contribute time to several periods. Observation ended at the earliest of KS diagnosis, last follow-up visit, death, or 8 years after cART start. We calculated KS incidence rates by dividing the number of patients developing KS by the number of person-year at risk and Poisson 95% confidence intervals (CIs). We fitted Cox models separately for each of the 6 periods, including in the models exposure group, origin, first-line regimen, calendar year of enrollment (4 categories), and the time-updated (current) variable CD4 cell count (6 categories), HIV-1 RNA viral load (4 categories), and age (4 categories). We used the likelihood ratio test to test whether hazard ratios (HRs) changed across time periods (test for interaction between period and risk factor).

In additional analyses we included baseline CD4 cell count or late presentation in the model, included square-root transformed CD4 cell counts and log-transformed HIV-1 RNA viral loads as continuous variables, and excluded the first 6 months after starting cART or patients enrolled into cohort before 2000. All analyses were done with Stata software, version 13 (StataCorp). Results are presented as medians with interquartile ranges (IQRs), incidence rates per 100 000 py, and crude and adjusted HRs, with 95% CIs.

RESULTS

Study Population

A total of 109 461 patients from 21 cohorts from 10 European countries (Austria, Belgium, Denmark, Germany, France, Italy, Spain, Greece, the Netherlands, and Switzerland) or the EuroSIDA study [16] were eligible for the current analyses. Supplementary Figure 1 shows the number of included and excluded patients. The main reasons for excluding patients were enrollment before 1996 (n = 52 717; 27%), patients who were not starting cART (n = 63 708; 32%), and patients who were not antiretroviral therapy naive at cART initiation (n = 34 644; 18%). A total of 9347 KS cases were excluded, of which 3872 (41%) were diagnosed before 1996. Of the post-1996 cases, 3414 (62%) were diagnosed within ≤30 days after cART initiation. Included and excluded patients were similar with respect to sex, age, and CD4 cell counts at enrollment (data on file). Included patients had higher HIV-1 RNA viral loads at enrollment than excluded patients (median, 75 000 vs 19 407 copies/mL in included vs excluded patients). Patients who enrolled before 2000 were more likely than those who enrolled later to have missing HIV-1 RNA measurements and thus to be excluded from the multivariable analysis.

The baseline characteristics of the 109 461 included patients are shown in Table 1: 40 972 (37%) were MSM, and 29 845 (27%) were women. The majority of patients (n = 84 514; 77%) were of European origin; 16 330 (15%) were of African origin. The median (IQR) age was 37.3 (31.2–44.7) years. The median (IQR) CD4 cell count was 250/μL (122–370/μL); 15 652 patients (14%) were in Centers for Disease Control and Prevention stage C. The median (IQR) follow-up since starting cART was 4.6 (2.0–8.0) years, and the total observation time was 501 700 py.

A total of 916 patients developed KS after starting cART. The median (IQR) time from starting cART to KS diagnosis was 223 (77–987) days. Patients with KS were more likely to be male, MSM, and enrolled during the early years of the cART era (1996–2000) than those remaining free of KS (Table 1). Among 318 heterosexual patients developing KS, 66% (211) were men and 34% (107) were women; 38% (124) were of

Table 1. Patient Characteristics at cART Initiation

Characteristic	Patients, No. (%)[a]	
	With KS (n = 916)	Without KS (n = 108 545)
Exposure group		
MSM	554 (60.5)	40 418 (37.2)
Heterosexual contact	211 (23.0)	32 142 (29.6)
Women	107 (11.7)	29 738 (27.4)
Unknown	44 (4.8)	6247 (5.8)
Origin		
Europe	713 (77.8)	83 801 (77.2)
Africa	146 (15.9)	16 184 (14.9)
North America	49 (5.3)	6284 (5.8)
Other	8 (0.9)	2276 (2.1)
Age, median (IQR), y	38 (32.1–46.4)	37.3 (31.2–44.7)
Age group		
16–30 y	152 (16.6)	22 256 (20.5)
31–40 y	366 (40.0)	43 238 (39.8)
41–50 y	233 (25.4)	27 903 (25.7)
>50 y	165 (18.0)	15 148 (14.0)
CD4 cell count, median (IQR), cells/μL	146 (43–302)	250 (124–370)
CD4 cell count		
<50/μL	224 (24.5)	12 278 (11.3)
50–99/μL	105 (11.5)	8104 (7.5)
100–199/μL	155 (16.9)	17 120 (15.8)
200–349/μL	188 (20.5)	31 793 (29.3)
350–499/μL	87 (9.5)	16 592 (15.3)
≥500/μL	62 (6.8)	10 952 (10.1)
Data missing	95 (10.4)	11 706 (10.8)
HIV RNA viral load, median (IQR), copies/mL	147 819 (50 000–384000)	75 000 (19 000–222 000)
HIV RNA viral load		
≥100 000 copies/mL	460 (50.2)	38 329 (35.3)
10 001–99 999 copies/mL	236 (25.8)	34 561 (31.8)
501–9999 copies/mL	48 (5.2)	12 322 (11.4)
≤500 copies/mL	3 (0.3)	1561 (1.4)
Data missing	169 (18.4)	21 772 (20.1)
CDC stage		
A/B	640 (69.9)	90 642 (83.5)
C	237 (25.9)	15 415 (14.2)
Data missing	39 (4.3)	2488 (2.3)
Late presentation		
No	231 (25.2)	42 096 (38.8)
Yes	649 (70.9)	60 753 (56.0)
Data missing	36 (3.9)	5696 (5.2)
First-line cART regimen		
Nonboosted PI	253 (27.6)	21 478 (19.8)
Boosted PI	334 (36.5)	37 918 (34.9)
NNRTI without PI	293 (32.0)	42 581 (39.2)
Other	36 (3.9)	6568 (6.1)
Calendar year of enrollment		
1996–2000	336 (36.7)	29 676 (27.3)
2001–2005	334 (36.5)	35 781 (33.0)
2006–2010	191 (20.9)	32 844 (30.3)
2011–2014	55 (6.0)	10 244 (9.4)

Abbreviations: cART, combination antiretroviral therapy; CDC, United States Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; IQR, interquartile range; KS, Kaposi sarcoma; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] Data represent No. (%) of patients unless otherwise specified.

African origin. Patients developing KS were often late presenters and started cART in a more advanced clinical stage than those not developing KS. In the 916 patients with KS, the CD4 cell count at KS diagnosis was <350/μL in 705 patients, 350–499/μL in 106, and ≥500/μL in 105. Patients with CD4 cell counts ≥350/μL at KS diagnosis were more likely to be MSM, to be older, and to have higher CD4 cell counts at enrollment than those with counts <350/μL at KS diagnosis. The median (IQR) viral load at KS diagnosis was 358 (0–27 750) copies/mL, and the median (IQR) CD4 cell count was 243/μL (107–409/μL) and 450/μL (280–596/μL) in those developing KS 30–90 days or 5–8 years, respectively, after starting cART. Four hundred eighteen (46%) of the KS cases were diagnosed during the first 6 months after starting cART; these patients had low baseline CD4 cell counts (median, 85/μL; IQR, 27–230/μL) and were often late presenters (n = 340; 81%).

Incidence Rates

The overall KS incidence rate was 183/100 000 py (95% CI, 171–195). It was 1472/100 000 py 30–90 days after cART initiation, declined to 582/100 000 at 91–180 days, 247/100 000 at 181 days to 1 year, and 120/100 000 at 1–2 years (Figure 1*A*). The rate was similar in the subsequent 2 periods: about 82–85/100 000 py at >2 years of cART initiation. Figure 1*B*–1*F* shows the incidence rate stratified by current CD4 cell count and HIV-1 RNA viral load, origin, exposure group, and current age. For incidence rates per risk group and time period, see Supplementary Table 1. In all periods after cART initiation, incidence rates were highest in patients with current CD4 cell counts <50/μL, in those with nonsuppressed HIV-1 RNA viral replication, and in MSM. More than 2 years after cART initiation, the KS incidence in MSM was about 149–160/100 000 py. The lowest rates were observed 5–8 years after cART initiation in women (23/100 000 py), in patients with suppressed viral load (41/100 000 py), and in patients with CD4 cell counts ≥500/μL (36/100 000 py).

Risk Factors by Period

A total of 100 022 patients (91.4%) had complete data and were included in the multivariable analyses. The HRs from the multivariable Cox models by period after cART initiation are shown in Table 2 and Supplementary Figure 2; results from univariable analyses are shown in Supplementary Tables 2 and 3. The risk of KS was increased in MSM, in patients of African origin, and in those with low current CD4 cell counts. The association was strongest for MSM (HR, 5.87 for MSM vs heterosexual men at 30–90 days after cART initiation) and for current CD4 cell count (HR, 7.37 for <50/μL vs 350–499/μL at 30–90 days). There was little evidence for a difference in HRs across the 6 periods for exposure group, origin, calendar year of enrollment, first-line cART regimen or current CD4 cell count, with *P* values of .12–.93 from tests of interaction (Table 2). The situation was different for current HIV-1 RNA viral load: there was no

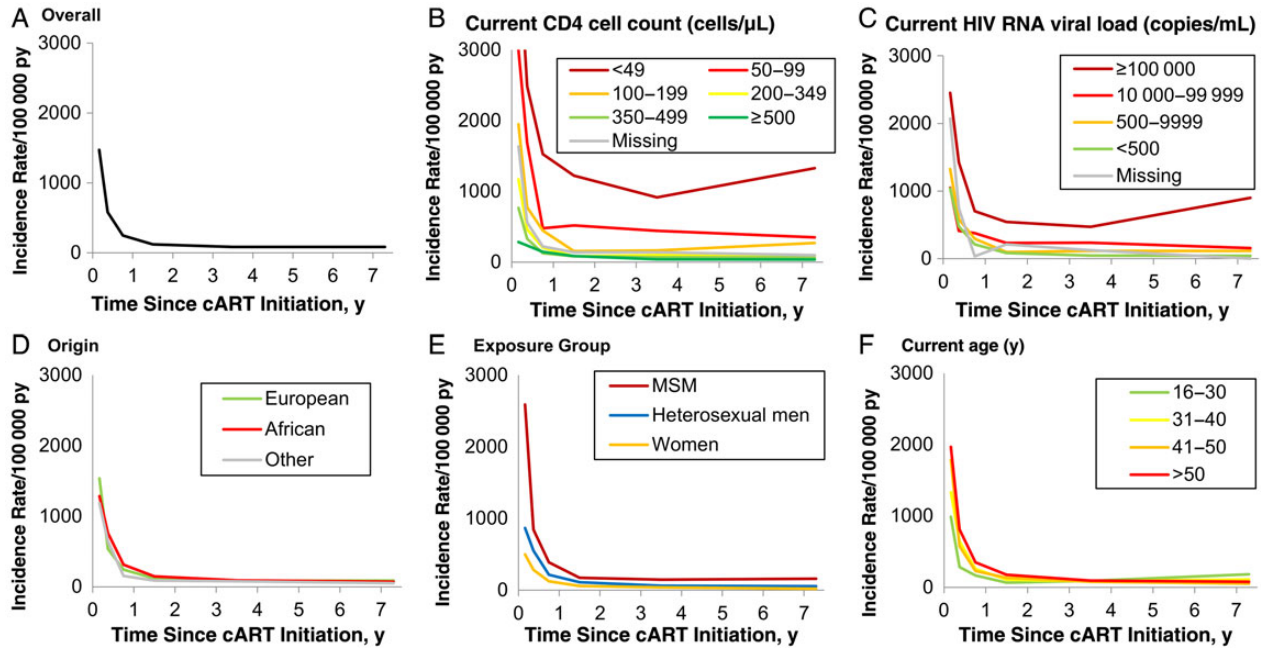

Figure 1. Kaposi sarcoma incidence rates overall and stratified for selected risk factors by time periods since start of combination antiretroviral therapy (cART). Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; py, person-years.

evidence of an association in the periods early after cART initiation, but an increasingly strong association emerged in the later periods ($P < .001$). The HR comparing viral loads ≥100 000 copies/mL with those ≤500 copies/mL was 3.08 (95% CI, 1.56–6.09) at 1–2 years after cART initiation and 9.72 (95% CI, 5.34–17.7) at 5–8 years.

In the overall multivariable analysis not stratified by time period (Supplementary Table 4), patients aged >50 years had a higher KS risk compared with those aged ≤30 years. There was some evidence for an interaction between current age and time since starting cART ($P = .07$). However, this finding was not robust in additional analyses (data on file). The baseline CD4 cell count (Supplementary Table 5) and late presentation (Supplementary Table 6) were associated with the risk of KS in the early periods after cART initiation but not thereafter. Results were similar when square-root-transformed current CD4 cell counts and log-transformed HIV-1 RNA viral loads were included as continuous variables rather than categories of current CD4 cell count and HIV-1 RNA viral load (data on file). Tests for interaction for current CD4 cell and current HIV RNA viral load were similar when we excluded the first 6 months after cART initiation ($P = .41$ and .004, respectively) and when we excluded patients enrolled before 2000 ($P = .49$ and <.001, respectively).

DISCUSSION

In this collaborative analysis, we found that the incidence rate of KS was about 1500/100 000 py in the first weeks after starting cART but declined thereafter to plateau at about 82–85/100 000 py after 2 years. In MSM the KS incidence rate was about 149–160/100 000 py, even 2 years after starting cART. This is higher than the age-standardized incidence of the most frequent cancers in the general population (breast and prostate cancer, 80/10 000 py and 70/10 000 py, respectively [17]). Other patient groups with high KS incidence rates were migrants from sub-Saharan Africa, late presenters, and patients with low CD4 cell counts. The lowest KS incidence rates were seen in heterosexual women who had started cART several years earlier. The strength of associations with KS in the different periods tended to be similar for most risk factors, with the exception of HIV-1 viral load. Viral load was not associated with KS up to 1 year after starting cART, but it emerged as an increasingly important risk factor thereafter.

Our analysis was based on a large European cohort collaboration including >100 000 patients and >500 000 py of follow-up with longitudinal measurements of CD4 cell count and HIV-1 RNA viral load and detailed information on origin, sexual orientation, and drug regimens. This is one of few studies in patients who have started cART ≥5 years earlier [2, 3] and, to the best of our knowledge, the first study to thoroughly examine changes in the importance of different risk factors over time since cART initiation, using time-updated values where appropriate. Our study has several limitations. Data on HHV-8 serostatus, KS stage, or KS-related IRIS were not available. For example, we could not assess whether the increased risk of KS during the first 6 months after cART initiation was related to IRIS [5]. The risk of unmasking IRIS is increased in patients

Table 2. Risk Factors for Developing KS by Time Since cART Initiation[a]

Risk Factor	HR (95% CI) by Time Since cART Initiation						*P* Value[b]
	30–90 d	91–180 d	6–12 mo	1–2 y	2–5 y	5–8 y	
Patients with KS/total, No.	201/90 789	130/91 646	116/90 511	93/85 735	156/75 503	94/48 498	
Exposure group							
MSM	5.87 (3.90–8.83)	2.84 (1.84–4.39)	3.32 (2.05–5.37)	3.00 (1.78–5.05)	4.17 (2.73–6.35)	4.43 (2.55–7.70)	.46
Heterosexual men (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	
Women	0.86 (.50–1.48)	0.54 (.30–.96)	0.62 (.33–1.16)	0.67 (.34–1.30)	0.65 (.37–1.13)	0.41 (.18–.95)	
Origin							
European (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	.93
African	2.01 (1.23–3.28)	2.07 (1.23–3.47)	2.22 (1.26–3.90)	2.21 (1.19–4.12)	1.96 (1.19–3.24)	1.69 (.84–3.40)	
Other	0.86 (.49–1.51)	1.53 (.84–2.80)	0.67 (.29–1.55)	1.22 (.52–2.89)	1.02 (.53–1.98)	0.65 (.23–1.83)	
Age group[c]							
16–30 y (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	.07
31–40 y	1.04 (.67–1.64)	2.01 (1.05–3.85)	1.37 (.75–2.50)	1.31 (.62–2.74)	0.92 (.54–1.59)	0.56 (.27–1.17)	
41–50 y	1.34 (.85–2.13)	1.70 (.85–3.39)	1.08 (.56–2.08)	1.65 (.77–3.52)	0.83 (.47–1.48)	0.28 (.13–.62)	
>50 y	1.52 (.92–2.51)	2.74 (1.35–5.58)	1.90 (.97–3.73)	2.42 (1.09–5.40)	1.21 (.66–2.22)	0.52 (.23–1.16)	
CD4 cell count[c]							
<50/μL	7.37 (4.26–12.7)	7.56 (3.85–14.8)	14.10 (6.68–29.8)	9.15 (4.06–20.6)	6.41 (3.40–12.1)	7.08 (3.32–15.1)	.50
50–99/μL	4.93 (2.77–8.80)	5.53 (2.86–10.7)	4.33 (1.90–9.88)	4.24 (1.79–10.0)	4.35 (2.18–8.68)	1.90 (.62–5.86)	
100–199/μL	3.46 (2.04–5.85)	2.89 (1.56–5.34)	4.16 (2.20–7.87)	1.43 (.66–3.11)	2.32 (1.31–4.11)	3.24 (1.60–6.54)	
200–349/μL	1.89 (1.13–3.14)	1.52 (.83–2.77)	1.62 (.84–3.12)	1.04 (.53–2.05)	1.45 (.89–2.36)	1.33 (.68–2.59)	
350–499/μL (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	
>500/μL	0.40 (.17–.94)	0.76 (.36–1.59)	1.05 (.53–2.07)	0.91 (.49–1.71)	0.62 (.38–1.00)	0.59 (.32–1.11)	
HIV RNA viral load[c]							
≥100 000 copies/mL	1.46 (.96–2.20)	1.65 (.99–2.75)	1.81 (.96–3.41)	3.08 (1.56–6.09)	5.34 (3.20–8.92)	9.72 (5.34–17.7)	<.001
10 001–99 999 copies/mL	1.04 (.65–1.68)	0.70 (.34–1.43)	1.51 (.77–2.96)	2.10 (1.07–4.12)	3.90 (2.46–6.19)	2.24 (1.11–4.53)	
501–9999 copies/mL	1.28 (.87–1.88)	1.04 (.65–1.66)	1.46 (.83–2.55)	0.95 (.46–1.97)	2.24 (1.35–3.73)	2.25 (1.13–4.46)	
≤500 copies/mL (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	
First-line cART regimen							
Nonboosted PI	0.53 (.32–.90)	0.82 (.46–1.46)	1.65 (.88–3.08)	0.86 (.46–1.62)	0.95 (.58–1.53)	0.91 (.49–1.68)	.12
Boosted PI (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	
NNRTI without PI	0.58 (.42–.81)	1.10 (.72–1.69)	1.05 (.66–1.65)	0.84 (.50–1.41)	0.90 (.60–1.36)	0.61 (.32–1.14)	
Other	0.50 (.22–1.15)	1.41 (.70–2.86)	1.21 (.50–2.90)	NA	0.35 (.13–.99)	0.52 (.18–1.54)	
Calendar year of enrollment							.39
1996–2000 (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	
2001–2005	1.20 (.77–1.89)	0.79 (.48–1.29)	1.84 (1.03–3.31)	0.60 (.34–1.08)	1.23 (.80–1.87)	0.99 (.57–1.71)	
2006–2010	0.88 (.53–1.44)	0.66 (.38–1.18)	1.77 (.91–3.43)	0.70 (.37–1.33)	0.77 (.42–1.41)	0.75 (.17–3.34)	
2011–2014	1.29 (.71–2.32)	1.01 (.46–2.21)	1.46 (.54–3.95)	NA	NA	NA	

Abbreviations: cART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; KS, Kaposi sarcoma; MSM, men who have sex with men; NA, not available; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; Ref, referent group.

[a] Results from multivariable Cox regression model, including only cases with no missing values for any of the covariates. Data represent HR (95% CI) unless otherwise specified; HRs are stratified by cohort and adjusted for exposure group, origin, current age, current CD4 cell counts, current HIV RNA viral loads, first-line cART regimen, and calendar period of enrollment.

[b] *P* value for change over time from test of interaction.

[c] Time-updated data.

with low CD4 cell count nadir at cART initiation [18], and previous studies have shown that timely initiation of cART at high CD4 cell counts may reduce the risk of developing unmasking IRIS-KS [18–20].

The most striking finding of our study is the emergence of HIV-1 RNA viral load as an increasingly strong risk factor for KS in patients who had started cART several years earlier. In this multivariable analysis the association between current HIV-1 RNA viral load and KS was independent of other risk factors, including immunodeficiency, and a dose-response relation was evident, with the highest risk of KS in those with viral loads ≥100 000 copies/mL. It therefore seems that soon after starting cART the incidence of KS is largely driven by immunodeficiency, whereas later on replicating HIV-1 and immunodeficiency independently contribute to the risk of KS. This might be explained by synergistic interactions between HIV and HHV-8 [21]. The HIV-1 Tat protein facilitates HHV-8 replication, which in turn may lead to an increased risk of KS [22, 23]. Likewise, HHV-8 has been shown to activate HIV replication [24]. Our results indicate that consistent long-term suppression of HIV-1 RNA replication may prevent such interactions and thus may reduce the risk of KS. These findings suggest that

monitoring viral load to detect treatment failures in a timely fashion might be important.

The KS incidence rates from this study are generally similar to estimates of previous studies [1–3] from Europe and the United States (see Supplementary Table 7). Our study confirms that MSM have a higher risk of developing KS than heterosexual men [10, 25–27], probably owing to the higher seroprevalence of HHV-8 infection, whereas women are at lower risk of developing KS than men [10, 27, 7]. This and other studies have shown that Europeans have lower KS incidence rates than migrants from sub-Saharan Africa [10, 28], which may again be explained by the higher HHV-8 seroprevalence in patients with African origins [6].

Previous studies have suggested that the risk of developing KS increases with age in patients who are not receiving cART [28] but not in patients who have started cART [2, 3, 28]. Our overall analysis not stratified by time period suggested an increased KS risk in patients aged >50 years compared with those aged ≤30 years. However, we did not observe a dose-response relationship, and there was no robust evidence for an interaction with time since starting cART.

In contrast to a 2015 study [29], our study did not show that boosted PI-based first-line regimens were associated with a lower risk of developing KS than NNRTI-based regimens. We cannot exclude the possibility that confounding by indication may have influenced our findings. Moreover, we examined the initial first-line regimen only and adopted an intention-to-continue-treatment approach, which ignored subsequent treatment changes and therefore limited our ability to detect associations of KS with different cART regimens. We found that low current CD4 cell counts increased the risk of developing KS in each period after starting cART, whereas baseline CD4 cell count or late presentation predicted KS in the first months after cART initiation only. This finding is in line with findings of a previous study [3], which showed that low baseline CD4 cell counts were associated with an increased risk of developing KS in the first 6 months after starting cART but not thereafter.

The risk of developing KS is particularly high in late presenters and patients with low current CD4 cell counts shortly after cART initiation. This observation might be explained by an increased vigilance of patients and physicians for signs of disease but also by unmasking IRIS-associated KS [20]. KS incidence and its associated risk factors in patients who started cART several years earlier is not completely understood. Our study confirms that low current CD4 cell count increases the risk of KS throughout all time periods after starting cART.

In conclusion, this collaborative analysis of European HIV cohort studies shows that in patients starting cART both incidence and risk factors for KS change with treatment duration. Whereas immunodeficiency is the dominant risk factor soon after starting cART, detectable HIV-1 RNA viral load becomes an increasingly important risk factor in patients who started cART several years earlier, independently of immunodeficiency. Further research is needed on the interaction between HIV-1 and HHV-8 replication and the risk of KS, and the potential impact of cART on HHV-8 viremia.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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