IMIT AMACS ECS-Mothers & ECS-Infants NSHPC-Mothers & NHPS-Infants PISCIS KOMPNET CASCADE ANRS CO2 SEROCO Frankfurt HIV Cohort Study San Raffaele ANRS CO1/CO10 EPF UK CHIC Athena ITLR-Mothers & ITLR-Infants Swiss HIV Cohort Study ICC ANRS CO6 PRIMO Co-RIS MOCHIV-Mothers & MoCHIV-Infants The Italian MASTER Cohort CHIPS ANRS CO4 French Hospital's Database on HIV HIV-MIP-Mothers & HIV-MIP-Infants GEMES-Haemo ANRS CO3 AQUITAINE EuroSIDA Madrid Cohort HIV Children VACH Modena Cohort Study Danish HIV Study ANRS CO8 COPILOTE ICONA St. Pierre

Collaboration of Observational HIV Epidemiological Research Europe

Coordination: Copenhagen HIV Programme (CHIP) & Institut de Santé Publique,d'Epidémiologie et de Développement (ISPED)

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Kaposi Sarcoma in the Era of Combined Antiretroviral Therapy

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BACKGROUND

- Combined antiretroviral therapy (cART) has reduced the risk of developing Kaposi Sarcoma (KS), however, the residual burden of disease remains unclear.
- We analyzed the data of a large prospective European multi-cohort project, the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) over a period of 15 years to examine risk factors at enrollment and KS incidence in the era of cART.

METHODS

The COHERE Collaboration

- COHERE is a collaboration of 33 cohorts from 30 European countries (see Box) coordinated by two regional centres in Bordeaux and Copenhagen.
- The contributing cohorts submit information on a restricted dataset using the HIV Cohort Data Exchange Protocol (HICDEP), including data on patient demographics, use of cART, CD4 counts and HIV RNA measurements, AIDS defining events and deaths. This study is based on the COHERE merger 2011.

Inclusion criteria & definitions

- HIV-infected patients who enrolled in a COHERE cohort after 1.1.1996 were included. Analysis was restricted to adult patients (> 16 years at enrollment) who had a documented cART treatment status (see Figure 1).
- cART was defined as a regimen of at least 3 drugs from at least 2 drug classes. KS cases diagnosed within 30 days after cART initiation were classified as not on cART.
- Patients with less than 30 days of follow-up time and patients developing KS within the first 30 days after enrollment (prevalent cases) where excluded from the study.

Statistical methods

- KS incidence rates were estimated for patients on cART and not on cART.
- Risk factors were estimated running Cox regression models adjusted for calendar period, age, exposure group, CD4 cell counts, HIV viral load and CDC stage at enrollment (model 1), and origin (model 2).
- Patient follow-up was censored on the date of the patient's last clinic visit.

Box: Cohorts participating in COHERE Collaboration

AMACS (Greece)	ICC (Italy)
ANRS CO1/CO10 EPF (France)	ICONA (Italy)
ANRS CO2 SEROCO (France)	IMIT (Italy)
ANRS CO3 AQUITAINE (France)	ITLR-Mothers & ITLR-Infants (Italy)
ANRS CO4 French Hospital's Database on HIV	KOMPNET (Germany)
ANRS CO6 PRIMO (France)	Madrid Cohort HIV Children (Spain)
ANRS CO8 COPILOTE (France)	MOCHIV-Mothers & MoCHIV-Infants (Switzerland)
ATHENA (Netherlands)	Modena Cohort Study (Italy)
CASCADE (Europe)	NSHPC-Mothers & NHPS-Infants (UK)
CHIPS (UK and Ireland)	PISCIS (Spain)
Co-RIS (Spain)	San Raffaele (Italy)
Danish HIV Study (Denmark)	Swiss HIV Cohort Study (SHCS, Switzerland)
ECS (Europe)	St. Pierre (Belgium)
EuroSIDA (Europe)	The Italian MASTER Cohort (Italy)
Frankfurt HIV Cohort Study (Germany)	VACH (Spain)
GEMES-Haemo (Spain)	UK CHIC (UK)
HIV-MIP-Mothers & HIV-MIP-Infants (Spain)	

RESULTS

Patient characteristics

- Of the 267,837 patients in the COHERE data set, 156,667 patients have fulfilled our inclusion criteria. Altogether 24 cohorts of the network contributed data to the current analysis (see Figure 1).
- Among the included patients 72% were male, median age at enrollment was 35 years and median CD4 cell count was 338 cells/µL.
- 25,564 patients never started any antiretroviral therapy; 23,342 patients started mono- or dual-therapy, which was followed by cART in 17,703 patients; and 107,761 patients started cART being treatment naïve (see Figure 2).
- During 877,920 person-years of observation 2,090 patients developed KS.

Figure 1: Flow diagram of the study population

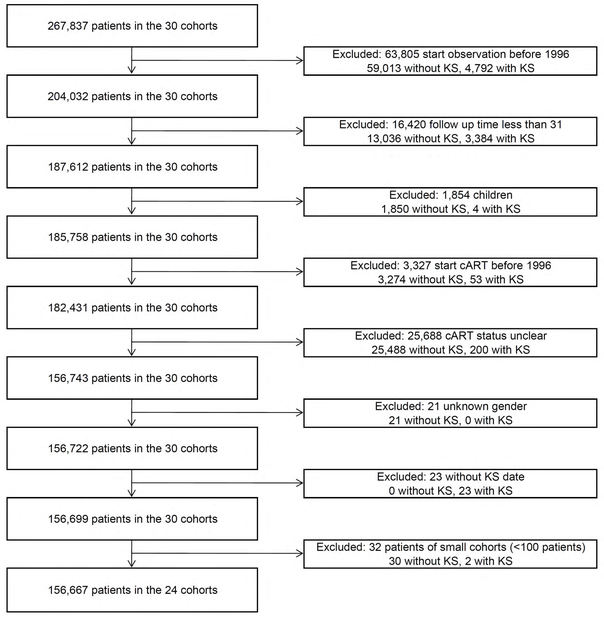


Figure 2: Distribution of patients (N=156,667) according to cART status before Kaposi Sarcoma diagnoses

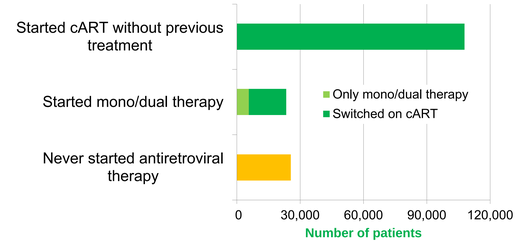


Table 1: Characteristics of HIV-infected patients developing and not developing Kaposi Sarcoma

		Patients with KS				Patients without KS		Total
		Not on cART*		On cART *				
All patients		**911**	**(100%)**	**1,179**	**(100%)**	**154,577**	**(100%)**	**156,667**
Gender	**Male**	**847**	**(93%)**	**1,054**	**(89%)**	**111,837**	**(72%)**	**113,738**
	Female	**64**	**(7%)**	**125**	**(11%)**	**42,740**	**(28%)**	**42,929**
Age (years)	**Missing**	**1**	**(<1%)**	**0**	**(<1%)**	**117**	**(<1%)**	**118**
	16-30	**193**	**(21%)**	**234**	**(20%)**	**39,996**	**(26%)**	**40,423**
	30-40	**402**	**(44%)**	**508**	**(43%)**	**65,848**	**(43%)**	**66,758**
	40-50	**213**	**(23%)**	**264**	**(22%)**	**32,572**	**(21%)**	**33,049**
	>50	**102**	**(11%)**	**173**	**(15%)**	**16,044**	**(10%)**	**16,319**
Year of enrolment	**1996-2000**	**358**	**(39%)**	**554**	**(47%)**	**48,405**	**(31%)**	**49,317**
	2001-2005	**410**	**(45%)**	**487**	**(41%)**	**65,838**	**(43%)**	**66,735**
	2006-2011	**143**	**(16%)**	**138**	**(12%)**	**40,334**	**(26%)**	**40,615**
Exposure group	**Homo/bisexual**	**645**	**(71%)**	**759**	**(64%)**	**59,214**	**(38%)**	**60,618**
	Hetero	**173**	**(19%)**	**277**	**(23%)**	**61,702**	**(40%)**	**62,152**
	Other	**51**	**(6%)**	**75**	**(6%)**	**22,747**	**(15%)**	**22,873**
	Unknown	**42**	**(5%)**	**68**	**(6%)**	**10,914**	**(7%)**	**11,024**
Origin	**Europe**	**554**	**(61%)**	**781**	**(66%)**	**96,550**	**(62%)**	**61,824**
	Africa	**62**	**(7%)**	**136**	**(12%)**	**16,102**	**(10%)**	**16,295**
	North America	**5**	**(1%)**	**4**	**(<1%)**	**500**	**(<1%)**	**509**
	Other	**49**	**(5%)**	**63**	**(5%)**	**10,503**	**(7%)**	**10,647**
	Unknown	**241**	**(26%)**	**195**	**(17%)**	**30,833**	**(20%)**	**67,392**
Ethnicity	**White**	**335**	**(37%)**	**344**	**(29%)**	**47,835**	**(31%)**	**48,514**
	Black	**54**	**(6%)**	**61**	**(5%)**	**12,084**	**(8%)**	**12,199**
	Other	**26**	**(3%)**	**13**	**(1%)**	**3,321**	**(2%)**	**3,360**
	Unknown	**496**	**(54%)**	**761**	**(65%)**	**91,337**	**(59%)**	**92,594**

* Kaposi Sarcoma (KS) cases diagnosed within 30 days after cART start were classified as not on cART

Incidence rates

- The incidence rate was 393/100,000 PYs (95% confidence interval [95% CI] 366-421) among patients not receiving cART.
- In the first 6 months of cART, the incidence rate was 976/100,000 PYs (95% CI 889-1070).
- Among patients on cART for more than 6 months the incidence rate was 123/100,000 PYs (95% CI 115-133) (see Figure 3).
- Homo/bisexual men, persons above 50 years of age, from African origin or Black ethnicity also tended to have higher incidence rates (data not shown).

Figure 3: Kaposi Sarcoma incidence rate by cART status
Per 100,000 person-years with 95% confidence interval (CI)

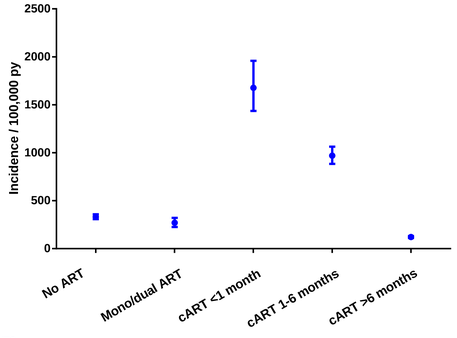


Table 2: Risk of developing KS: results from multivariate Cox regressions

		Model 1 (1422 KS/103,411 patients[1])			Model 2 (1180 KS/85,187 patients[1])		
		HR	(95% CI)	p-value	HR	(95% CI)	p-value
Treatment	No treatment	1.00		<0.0001	1.00		<0.0001
	Mono/dual therapy	0.54	(0.41-0.70)		0.58	(0.43-0.76)	
	cART (30-180 days)	1.32	(1.13-1.54)		1.34	(1.12-1.59)	
	cART (>180 days)	0.21	(0.18-0.25)		0.23	(0.19-0.28)	
Year of enrolment	1996-2000	1.37	(1.16-1.62)	0.001	1.38	(1.14-1.66)	0.003
	2001-2005	1.20	(1.02-1.40)		1.24	(1.04-1.47)	
	2006-2011	1.00			1.00		
Exposure group	Homo/bisexual men	3.05	(2.66-3.50)	<0.0001	3.55	(3.04-4.14)	<0.0001
	Other men	1.00			1.00		
	Women	0.57	(0.46-0.71)		0.48	(0.38-0.61)	
Age (years)*	16-30	1.00		<0.0001	1.00		<0.0001
	30-40	1.12	(0.97-1.29)		1.10	(0.94-1.29)	
	40-50	1.23	(1.05-1.45)		1.18	(0.99-1.41)	
	>50	1.65	(1.37-1.98)		1.75	(1.43-2.12)	
CD4 count (cells/µl)*	<49	2.68	(2.19-3.28)	<0.0001	2.50	(2.01-3.13)	<0.0001
	50-99	1.99	(1.58-2.51)		1.83	(1.42-2.37)	
	100-199	1.41	(1.15-1.73)		1.29	(1.03-1.62)	
	200-349	1.19	(1.00-1.40)		1.12	(0.93-1.34)	
	350-499	1.00			1.00		
	500-599	0.91	(0.74-1.12)		0.95	(0.76-1.20)	
	>600	0.77	(0.64-0.92)		0.81	(0.67-0.99)	
HIV RNA (copies/mL)*	>=100000	3.21	(2.04-5.05)	<0.0001	3.49	(2.10-5.79)	<0.0001
	10'000-99'999	2.15	(1.37-3.38)		2.31	(1.40-3.82)	
	501-9999	1.18	(0.74-1.87)		1.24	(0.73-2.08)	
	>=500	1.00			1.00		
CDC stage*	A/B	0.96	(0.81-1.12)	0.58	0.99	(0.83-1.18)	0.94
	C	1.00			1.00		
Origin	European				1.00		<0.0001
	African				2.47	(2.01-3.04)	
	Other				1.18	(0.96-1.46)	

[1] Only patients with no missing values for any of the explanatory variable have been included into the Cox-Model

* Values assessed at the time of enrolment

cART: Combination antiretroviral therapy

Risk factors

- The risk of developing KS was lower among patients on stable treatment (over 6 months) (HR 0.21, 95% CI 0.18-0.25; model 1) when compared to patients who did not receive treatment.
- The risk of developing KS was higher among patients aged > 50 years, among men, and men who have sex with men.
- The risk of developing KS is higher among patients with low CD4 counts and high HIV viral loads at enrollment (Table 1).
- However, there was no evidence for an effect of CDC stage at enrollment on the risk of developing KS.
- Model 2 confirms these results and indicates a higher risk for patients of African origin.

SUMMARY AND CONCLUSIONS

- In the era of cART the incidence rate of KS remains high during the first months on cART, possibly because of IRIS.
- Male patients, particularly men who have sex with men, patients of African origin or aged above 50 years are important risk groups.
- Patients aged above 50 and patients with uncontrolled HIV viral replication and advanced immunosuppression are also at increased risk of developing KS.
- Male patients, particularly men who have sex with men (MSM), and patients of African origin are at increased risk of developing KS. This may reflect the underlying prevalence of HHV-8 infection, which tends to be high in MSM and patients of African origin.

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