IMPACT OF UNIVERSAL ART ACCESS ON KAPOSI SARCOMA: RESULTS FROM THE ICONA COHORT

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CROI 2020 Boston, March 8–11, 2020

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BACKGROUND

The widespread introduction of effective antiretrovirals (ART) to control HIV dramatically decreased the burden of AIDS-related Kaposi Sarcoma (KS). However, KS remains the second most frequent tumor in patients infected with HIV in the world, being the most common cancer in sub-Saharan Africa.

The clinical course of KS can range from an indolent state to a severe, progressive disease leading to significant morbidity and mortality. ART is essential for HIV-infected KS patients, but despite ART, up to a third of KS patients have disease recurrence or do not respond to ART alone. Moreover, KS also develops in HIV patients despite ART, i.e., in patients with no detectable HIV load and near-normal CD4 levels.

Our aim was to define trends in incidence/prevalence of KS, outcome and associated factors in a large Italian cohort of HIV-infected patients.

METHODS

We included naïve HIV-infected individuals (PLHIV) enrolled in the ICONA cohort over 1997-2019.

Prevalent cases were PLHIV with a diagnosis of KS prior and up to 30 days after enrolment.

Incident cases were defined as new KS diagnoses occurring after ART initiation.

Patients' characteristics at the date of enrolment were compared by prevalent KS status and associations identified by logistic regression modelling.

In the subset of people KS-free at enrolment, standard Kaplan-Meier curves were used to model time from ART initiation to development of KS and a Cox regression model to identify factors associated with this outcome. A similar analysis was performed in PLHIV with prevalent KS to identify factors associated with their risk of KS relapse or death after ART (clinical failure).

RESULTS

Among 17,742 PLHIV enrolled in the ICONA cohort over 1997-2019, 248 prevalent KS cases and 36 incident KS cases were identified. Characteristics of prevalent cases are shown in table 1.

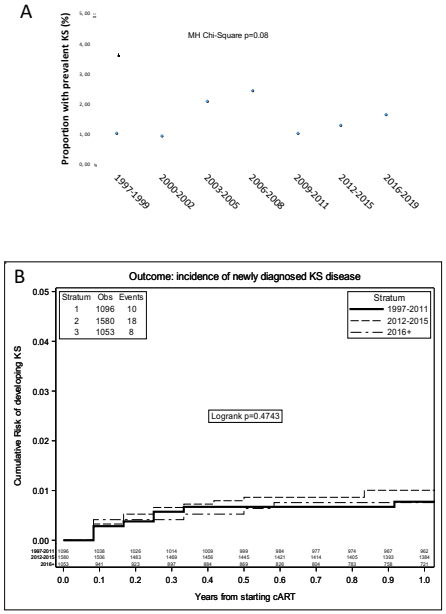
Table 1. Characteristics at enrolment by KS diagnosis

Characteristics at enrolment	Yes	No	p-value*	Total
	N= 248	N= 17494		N= 17742
Gender, n(%)			<.001	
Female	17 (6.9%)	4090 (23.4%)		4107 (23.1%)
Mode of HIV Transmission, n(%)			<.001	
PWID	13 (5.2%)	3173 (18.1%)		3186 (18.0%)
MSM	131 (52.8%)	6626 (37.9%)		6757 (38.1%)
Heterosexual contacts	85 (34.3%)	6595 (37.7%)		6680 (37.6%)
Other/Unknown	19 (7.7%)	1100 (6.3%)		1119 (6.3%)
Nationality, n(%)			0.590	
Not Italian	61 (24.6%)	4525 (25.9%)		4586 (25.8%)
AIDS diagnosis (not KS), n(%)			<.001	
Yes	186 (75.0%)	1622 (9.3%)		1808 (10.2%)
CVD diagnosis, n(%)			0.799	
Yes	1 (0.4%)	91 (0.5%)		92 (0.5%)
HBsAg, n(%)			0.286	
Negative	209 (84.3%)	14155 (80.9%)		14364 (80.9%)
Positive	4 (1.6%)	220 (1.3%)		224 (1.3%)
Not tested	35 (14.1%)	3122 (17.8%)		3157 (17.8%)
HCVAb, n(%)			<.001	
Negative	196 (79.0%)	11415 (65.2%)		11611 (65.4%)
Positive	18 (7.3%)	3252 (18.6%)		3270 (18.4%)
Not tested	34 (13.7%)	2830 (16.2%)		2864 (16.1%)
Hepatitis co-infection*, n(%)			<.001	
No	186 (75.0%)	10752 (61.5%)		10938 (61.6%)
Yes	22 (8.9%)	3412 (19.5%)		3434 (19.4%)
Not tested	40 (16.1%)	3333 (19.0%)		3373 (19.0%)
Calendar year of baseline**			0.085	
Median (IQR)	2011 (2003, 2014)	2012 (2003, 2015)		2012 (2003, 2015)
Age, years			<.001	
Median (IQR)	45 (37, 53)	42 (32, 49)		42 (32, 49)
CD4 count, cells/mmc			<.001	
Median (IQR)	70 (26, 190)	391 (196, 581)		387 (189, 578)
CD4 count nadir, cells/mmc			<.001	
Median (IQR)	76 (24, 193)	392 (200, 581)		389 (194, 578)
CD8 count, cells/mmc			<.001	
Median (IQR)	692 (450, 1031)	871 (601, 1243)		868 (598, 1241)
Viral load, log10 copies/mL			<.001	
Median (range)	5.29 (0.00, 7.00)	4.57 (0.00, 8.00)		4.58 (0.00, 8.00)
Median (IQR)	5.29 (4.81, 5.67)	4.57 (3.88, 5.18)	0.099	4.58 (3.89, 5.18)
Smoking, n(%)			<.001	
No	104 (41.9%)	4992 (28.5%)		5096 (28.7%)
Yes	49 (19.8%)	4533 (25.9%)		4582 (25.8%)
Unknown	95 (38.3%)	7972 (45.6%)		8067 (45.5%)
CD4 count, n(%)			<.001	
<=200 cells/mmc	170 (77.6%)	3899 (25.5%)		4069 (26.3%)
Time from HIV diagnosis, months				
Median (IQR)	1 (0, 2)	2 (0, 26)		2 (0, 25)

*Chi-square or Kruskal-Wallis test as appropriate

No significant differences in prevalence (by year of enrolment) and incidence (by year of ART initiation) of KS were observed (Figure).

Figure: Trends in prevalence(A) and incidence (B) of KS



At multivariable logistic regression, the only factor independently associated with **prevalent KS** was **mode of HIV transmission** (MSM versus PWID, adjusted [aOR]: 5.24 (1.35, 20,39)), as shown in Table 2.

Table 2. OR of prevalent KS diagnosis from fitting a logistic regression model

	Logistic regression estimates of factors associated with prevalent KS				
	Unadjusted		Adjusted*		
Factor	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Type III p-value
Mode of HIV Transmission					<.001
MSM vs. PWID	4.83 (2.72, 8.55)	<.001	5.24 (1.35, 20.39)	0.017	
Heterosexual vs. PWID	3.15 (1.75, 5.65)	<.001	2.50 (0.65, 9.57)	0.182	
Other/Unknown vs PWID	4.22 (2.08, 8.56)	<.001	2.24 (0.48, 10.56)	0.306	
Age, years					
per 10 older	1.32 (1.19, 1.47)	<.001	1.23 (1.00, 1.53)	0.051	
AIDS diagnosis (not KS)					
Yes vs. No	29.36 (21.93, 39.32)	<.001	49.39 (29.32, 83.21)	<.001	
HBsAg					
Positive vs . Negative	1.29 (0.48, 3.49)	0.619	1.24 (0.13, 11.75)	0.852	
HCVAb					
Positive vs . Negative	0.34 (0.21, 0.55)	<.001	0.55 (0.20, 1.55)	0.258	
CD8 count, cells/mmc					
per 100 higher	0.93 (0.90, 0.96)	<.001	1.02 (0.99, 1.05)	0.238	
Site geographical position					0.084
Center vs. North	1.15 (0.89, 1.50)	0.285	1.19 (0.75, 1.91)	0.461	
South vs. North	0.68 (0.42, 1.11)	0.125	0.60 (0.28, 1.27)	0.181	
Smoking					
Yes vs. No	0.70 (0.51, 0.96)	0.029	0.73 (0.43, 1.22)	0.228	

*Multivariable model includes all variables selected bybackward selection that were retained with a p-value less than 0.3 level

MAIN FINDINGS

Mode of HIV transmission is independently associated with both **prevalent** and **incidental cases.**

Pre-ART CD4+ count is strongly associated with **incidence** of KS in ART-treated PLHIV.

In contrast, factors independently associated with the risk of **incident** KS were **pre-ART CD4+ count** (adjusted relative hazard (aHR): 0.57 (0.42, 0.77) for 100 cells/mmc higher) and **mode of HIV transmission** (MSM versus HS, aHR: 3.82 (1.62, 9.02)), as shown in Table 3.

Table 3. RH of incident KS diagnosis from fitting a Cox regression model

	Unadjusted and adjusted relative hazards of devoliping KS			
	Unadjusted RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
Baseline anchor drug class	1.00		1.00	
INSTI	0.81 (0.29, 2.25)	0.685	2.07 (0.53, 8.14)	0.297
NNRTI	1.40 (0.61, 3.20)	0.424	1.71 (0.56, 5.21)	0.343
PI/r				
Calendar period of starting ART				
1997-2011	1.66 (0.72, 3.84)	0.233	1.76 (0.66, 4.68)	0.257
2012-2015	1.32 (0.49, 3.58)	0.584	2.09 (0.57, 7.63)	0.267
2016+				
Age	1.33 (1.02, 1.74)	0.035	1.27 (0.92, 1.76)	0.149
per 10 years older				
Mode of HIV transmission	1.00		1.00	
Heterosexuals	0.63 (0.08, 4.96)	0.659	0.75 (0.09, 6.05)	0.786
PWID	2.74 (1.26, 5.96)	0.011	3.82 (1.62, 9.02)	0.002
MSM	2.52 (0.77, 8.18)	0.125	1.71 (0.36, 8.12)	0.497
Other				
Pre-ART CD4 count, cells/mm3	0.61 (0.47, 0.80)	<.001	0.57 (0.42, 0.77)	<.001
per 100 higher				
Pre-ART VL, copies/mL	1.29 (0.89, 1.87)	0.184	0.94 (0.63, 1.41)	0.772
per log10 higher				

*adjusted for age, mode of transmission andbaseline CD4 count and viral load

Over 1,316 PYFU, clinical failure after ART introduction was observed in 52 prevalent cases (29 deaths and 23 relapses) with an incidence rate of 3.9% (95% CI: 2.9-5.1). However, none of the considered factors showed an association with the risk of clinical failure.

CONCLUSIONS

Despite universal ART access, we did not observe a reduction of KS prevalence and incidence in recent years. The strong association of pre-ART CD4+ count with incidence of KS in ART-treated PLHIV strengthens the role of immune competence in KS. Further KSHV and HIV immune-virological characterization is warranted to better identify factors associated with KS occurrence in PLHIV.

FUNDING

ICONA Foundation is supported by unrestricted grants from Gilead Sciences, Janssen, MSD and ViiV Healthcare

ACKNOWLEDGMENTS

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