The Effect of Protease Inhibitor Use on Kaposi Sarcoma Incidence in a cART-Experienced Cohort

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BACKGROUND

- Although the incidence of Kaposi Sarcoma (KS) among HIV-infected patients has drastically decreased in the CART era, it remains the most common AIDS-associated cancer.[1]
- Protease inhibitors (PI) have been shown to have antitumor and antiangiogenic properties.[2]
- It is unknown if the use PI has an effect on the incidence of KS in HIV.
- The impact of timing after initiating specific CART medication classes on the incidence of KS remains unclear.

STUDY AIMS

- Determine the effect of CART initiation on the incidence of KS in HIV.
- Determine other risk factors, including PI utilization associated with SCCA in HIV

METHODS

- **Study design:** Retrospective cohort.
- **Data source:** VA Immunologic Case Registry
- **Study period:** 1985-2010.
- **Outcome of interest:** Incidence of HIV-associated KS.
- **Data analysis:**
- Descriptive analysis, univariate Chi-Square
- Percent of time on drug class: ratio total time on drug class/overall time on cART.
- Poisson multivariable model to analyze associated factors.
- Multivariate analysis further stratified by duration of time on CART
- Kaplan Meier Curve of KS incidence by time on drug class

DEFINITIONS

- **cART:** any combination of 2 NRTI and 1 of either NNRTI or PI.
- **Recent CD4 count:** CD4 count at time of event, death or censor.
- **Last HIV VL:** VL at time of event, death or censor.
- **Undetectable VL:** ≤500
- **KS:** ICD-9 codes 176.0-176.9, excluding prevalent cases (up to cases diagnosed 3 months after CART initiation)

RESULTS

- 25,529 HIV-infected veterans.
- KS incidence: 544 cases in 160,036 person-years (2.99/1,000 age-adjusted incidence)
- The incidence of KS is significantly higher in the first 2 years after initiating CART.
- Overall time on all drug classes decreases KS incidence.
- After 3 years on CART, individuals with >80% time on boosted PIs have a lower incidence of KS.

Figure 1: Flow chart of selection criteria to generate final cohort of HIV-infected veterans

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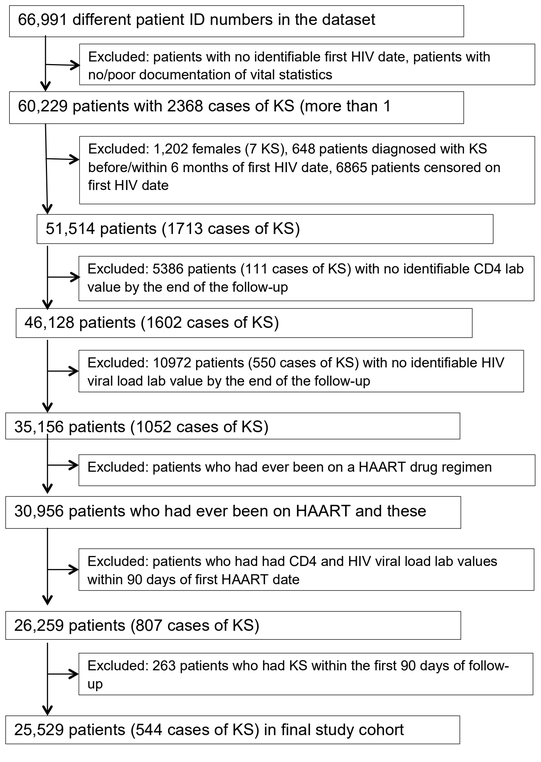


[1] Shiels M et al. J Natl Cancer Inst 2012.
[2] Gantt S et al. Curr Opin Oncol 2013.
[3] Letang E et al. AIDS 2013.
[4] Achenbach C et al. CID 2012.

Table 1: Characteristics of individuals in total cohort

Table 1: Characteristics of 25,529 individuals ever receiving cART

	Overall N=25529	*KS N=544*	*No KS N=24985*	*p-value*
	N (%)	N (%)	N (%)	
Follow-up duration (in years; mean (SD))	6.2 (4.2)	3.3 (2.9)	6.3 (4.2)	<0.0001
CART use (mean (SD))				
% PI	56.6 (41.8)	70.7 (35.7)	56.3 (41.9)	<0.0001
% Boosted PI	10.5 (18.5)	11.7 (20.3)	10.4 (18.4)	0.14
% Nelfinavir	10.9 (25.1)	22.7 (34.7)	10.7 (24.8)	<0.0001
% NNRTI	45.0 (41.7)	34.4 (37.3)	45.2 (41.8)	<0.0001
Age at HIV diagnosis (mean(SD))	44.6 (10.4)	40.2 (9.8)	44.7 (10.4)	<0.0001
Race/ethnicity				0.01
White	9549 (37.4)	206 (37.9)	9343 (37.4)	
African American	12911 (50.6)	281 (51.7)	12630 (50.5)	
Hispanic	1895 (7.4)	47 (8.6)	1848 (7.4)	
Unknown/Other	1174 (4.6)	10 (1.8)	1164 (4.7)	
Era of HIV diagnosis				<0.0001
Pre-CART (Before 1996)	6933 (27.2)	251 (46.1)	6682 (26.7)	
Early CART (1996-2001)	9059 (35.5)	236 (43.4)	8823 (35.3)	
Late CART (2002-2010)	9537 (37.3)	57 (10.5)	9480 (37.9)	
Use of IV drugs				0.26
No	16559 (64.9)	341 (62.7)	16218 (65.0)	
Yes	8940 (35.1)	203 (37.3)	8737 (35.0)	
DEYO co-morbidity score				0.05
0	13345 (52.5)	257 (47.4)	13088 (52.6)	
1	7453 (29.3)	173 (31.9)	7280 (29.3)	
2 and above	4609 (18.2)	112 (20.7)	4497 (18.1)	
Nadir CD4 count prior to CART				<0.0001
CD4 < 200	11220 (44.2)	295 (54.4)	10925 (43.9)	
CD4 200-350	7220 (28.4)	141 (26.0)	7079 (28.5)	
CD4 > 350	6967 (27.4)	106 (19.6)	6861 (27.6)	
CD4 count at event/censor				<0.0001
CD4 < 200	6382 (25.2)	271 (50.1)	6111 (24.6)	
CD4 200-350	4741 (18.7)	101 (18.9)	4640 (18.7)	
CD4 > 350	14233 (56.1)	162 (30.3)	14071 (56.7)	
% Undetectable HIV viral load at event/censor				<0.0001
< 40%	7834 (30.8)	375 (69.2)	7459 (30.0)	
40-80%	6352 (25.0)	90 (16.6)	6262 (25.2)	
> 80%	11244 (44.2)	77 (14.2)	11167 (44.8)	

*SD=standard deviation

Table 2. Multivariate Cox Regression Analyses

Table 2: Multivariable Poisson Model evaluating Time on CART

Parameter	Incidence Rate Ratio (CI)	P-value
Age at HIV Diagnosis		
<30	1.0 ref	
30-39	0.810 (0.609 - 1.075)	0.1449
40-49	0.575 (0.428 - 0.772)	0.0002
50-59	0.599 (0.421 - 0.850)	0.0042
60+	0.658 (0.406 - 1.068)	0.0905
Race		
White	1.0 ref	
Black	0.927 (0.768 - 1.119)	0.4321
Hispanic	1.047 (0.758 - 1.448)	0.7788
Other	0.722 (0.379 - 1.374)	0.3207
Deyo Score		
0	1.0 ref	
1	0.899 (0.738 - 1.095)	0.2903
2	0.956 (0.759 - 1.206)	0.7065
% of time on CART		
<80% time on CART	1.0 ref	
80-100% time on CART	1.426 (0.934 - 2.177)	0.1004
Era of HIV Diagnosis		
Pre-1996	1.0 ref	
1996-2002	0.859 (0.713 - 1.035)	0.1095
2003-2010	0.381 (0.264 - 0.551)	<.0001
CD4 count at Event/Censor		
<200	1.0 ref	
200-350	0.405 (0.319 - 0.514)	<.0001
>350	0.316 (0.246 - 0.406)	<.0001
HIV Viral Load		
Undetectable <80%	1.0 ref	
Undetectable 80-100%	0.462 (0.378 - 0.565)	<.0001
Time from Initiating CART		<.0001
Greater than 3 years	1.0 ref	
2-3 years	1.274 (0.965 - 1.681)	0.0874
1-2 years	1.577 (1.228 - 2.024)	0.0004
<1 year	1.798 (1.430 - 2.262)	<.0001

Tables 3-6. Multivariate Poisson analyses – Stratified by Specific Drug Utilization and Time since starting CART

Table 4: Multivariate Model* Duration of Non-nucleoside reverse transcriptase inhibitor class (NNRTI) Utilization and Percent of time on NNRTI

Percent of time on NNRTI	Incidence Risk Ratio (IRR)	p-value
In Year 1		
NNRTI <80%	1.0 ref	
NNRTI 80-100%	0.891 (0.612 - 1.297)	0.5483
In Year 2		
NNRTI <80%	1.0 ref	
NNRTI 80-100%	1.347 (0.887 - 2.044)	0.1618
In Year 3+		
NNRTI <80%	1.0 ref	
NNRTI 80-100%	1.036 (0.823 - 1.303)	0.7663

Table 3: Multivariate Model* Duration of boosted PI class (bPI) Utilization and Percent of time on bPI

Percent of time on bPI	Incidence Risk Ratio (IRR)	p-value
In Year 1		
bPI <80%	1.0 ref	
bPI 80-100%	1.049 (0.528 - 2.082)	0.8922
In Year 2		
bPI <80%	1.0 ref	
bPI 80-100%	0.982 (0.452 - 2.130)	0.9624
In Year 3+		
bPI <80%	1.0 ref	
bPI 80-100%	0.599 (0.436 - 0.824)	0.0016

Table 5: Multivariate Model* Duration of Nelfinavir Utilization and Percent of time on Nelfinavir

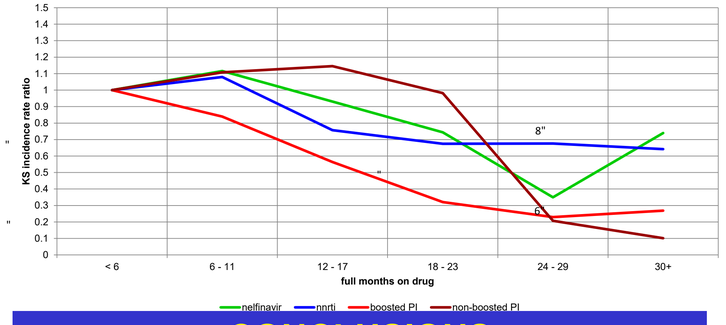
Percent of time on Nelfinavir	Incidence Risk Ratio (IRR)	p-value
In Year 1		
Nelfinavir <80%	1.0 ref	
Nelfinavir 80-100%	1.144 (0.766 - 1.707)	0.5110
In Year 2		
Nelfinavir <80%	1.0 ref	
Nelfinavir 80-100%	1.119 (0.721 - 1.739)	0.6156
In Year 3+		
Nelfinavir <80%	1.0 ref	
Nelfinavir 80-100%	1.121 (0.886 - 1.417)	0.3406

Table 6: Multivariate Model* Duration of Non-boosted PI (nbPI) Utilization and Percent of time on nbPI

Percent of time on nbPI	Incidence Risk Ratio (IRR)	p-value
In Year 1		
nbPI <80%	1.0 ref	
nbPI 80-100%	1.651 (0.998 - 2.733)	0.0509
In Year 2		
nbPI <80%	1.0 ref	
nbPI 80-100%	1.425 (0.830 - 2.447)	0.1984
In Year 3+		
nbPI <80%	1.0 ref	
nbPI 80-100%	1.093 (0.806 - 1.481)	0.5672

*Multivariate Models Adjusted for: Age, Race, Deyo Score, % time on CART, Era of HIV diagnosis, CD4 count, and HIV viral load

Figure 2. SCCA Incidence Rate Ratios, by length of Drug Class Use



CONCLUSIONS

- In our study, HIV-infected individuals were at the highest risk for KS within the first 2 years of CART initiation, consistent with an IRIS effect, as has been demonstrated by others.[3,4]
- Because of this possible IRIS effect, it is important to evaluate the effect of protease inhibitors several years after CART initiation.
- After 3 years of CART duration, individuals with >80% time on boosted PIs had a significant decrease in KS incidence, in contrast to individuals with >80% on other types of meds (non-boosted PI's, NNRTI's and Nelfinavir.
- Boosted PIs, as a drug class, may have a specific protective effect on KS incidence, that is independent of the effects of immune reconstitution from HIV viral load suppression.