Anal cancer risk and use of protease inhibitor: a nested case-control study within the ANRS CO4-FHDH cohort

P178

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Background

Several cohort studies have shown an increased risk of anal cancer associated with protease inhibitor (PI) use[(1-3)]. However, the analyses were often not adjusted for CD4 nadir, while it is associated both with the risk of anal cancer and ARV treatment initiated with a PI based regimen at treatment initiation, nor adjusted for the whole ARV treatment history.

Objective

We aimed at studying the associations between anal cancer risk and ARV uses conducting a nested case-control study.

Methods

Studied Population:

65956 PLHIV (**P**eople **L**iving with **HIV**) from ANRS CO4-FHDH[4], **F**rench **H**ospital **D**atabase on **H**IV (164 anal cancer / 65792 without anal cancer), followed up between 1997-2008, with **pVL (plasma HIV RNA) measurement and CD4 cell count**

- at **treatment** for ARV treated PLHIV
- **at anal cancer before 12/31/2008** (**index date**) for PLHIV with anal cancer and **12/31/2008** for those without anal cancer, for non ARV treated PLHIV .

Cases:

- Incident anal cancer occurring between 1997-2008 validated on histology [5]

Controls:

- Up to five controls fulfilling matching criteria were selected using incidence density sampling method

Matching criteria:

- Same age (±3 years) and sex-transmission groups (MSM, other men, women)
- Same period of inclusion in FHDH (<=1997/>1997)
- Followed at the time of index date (± 3 months)
- With available CD4 (-6 months/+1 month) and pVL (-6 months/+ 15 days) at index date
- Same region of care and preferably same center of care

Statistical methods:

- Principle of analyze: several conditional logistic regression analyses were adjusted for the same pool of variables and **with or without** additional adjustment for **CD4 cell count nadir** at treatment initiation or index date if not treated and for **cumulative duration of NRTI use.**

Tested Models:

Multivariable model 1 (MV1) adjusted for:

- Geographic origin,
- AIDS stage,
- Hepatitis B and hepatitis C infections,
- Viral load (VL) at index date,
- Cumulative duration of PI, NNRTI, and other treatment use per 5 years of exposure

Multivariable model 2 (MV2) adjusted for the same variables than in MV1 and additional adjustment for:

- CD4 cell count nadir at treatment initiation or index date if not treated

Multivariable model 3 (MV3) adjusted for the same variables than in MV1 and additional adjustment for:

- Cumulative duration of NRTI use.

Multivariable model 4 (MV4) adjusted for the same variables than in MV1 and additional adjustment for:

- CD4 cell count nadir at treatment initiation or index date if not treated
- and cumulative duration of NRTI use

Results

Figure 1. Flow-chart

71638 PLHIV ARV naïve at **ANRS CO4-FHDH** inclusion,

followed up between 1997-2008,

with pVL measurement before index date for PLHIV with anal cancer and before 12/31/2008 for PLHIV without anal cancer:
213 PLHIV with **anal cancer/71425** PLHIV **without anal cancer**

↓

65989 PLHIV with detailed ARV history
and **known CD4 cell count** at treatment if treated
or if not treated, at index date before 12/31/2008 for PLHIV with anal cancer and 12/31/2008 for PLHIV without anal cancer :
197 PLHIV with **anal cancer / 65792** PLHIV **without anal cancer**

↓

65956 PLHIV with CD4 and pVL measurements at anal cancer:
164 PLHIV with **anal cancer / 65792** PLHIV **without anal cancer**

Table 1. Characteristics of cases and controls PLHIV

	Cases (Anal cancer) N=164	Controls N=816
Sex and transmission groups		
MSM	106 (64.6)	526 (64.5)
Other Men	46 (28.0)	230 (28.2)
Women	12 (7.3)	60 (7.4)
Age at FHDH inclusion	34.6 (30.6-43.4)	35.9 (29.4-42.7)
Age at Index date*	45.0 (38.6-50.3)	44.4 (38.3-50.4)
Year of FHDH inclusion	1994 (1992-1996)	1994 (1992-1996)
Geographic Origin		
France	154 (93.9)	744 (91.2)
Sub-Saharan Africa	3 (1.8)	36 (4.4)
Other	7 (4.3)	36 (4.4)
Year of HIV diagnosis	1990 (1987-1994)	1992 (1989-1995)
Year of anal cancer	2003 (2001-2006)	
Hepatitis B antigen positive	21 (12.8)	57 (7.0)
Hepatitis C antibodies positive	21 (12.8)	130 (15.9)
AIDS stage	42 (25.6)	108 (13.2)
CD4 cell count nadir (/mm³) at treatment or index date if not treated	173 (76-271)	294 (180-400)
[0,100]	50 (30.5)	132 (16.2)
]100,200]	52 (31.7)	97 (11.9)
]200,350]	43 (26.2)	294 (36.0)
>350	19 (11.6)	293 (35.9)
CD4 cell count(/mm³) at index date *	320 (204-491)	490 (346-681)
pVL(copies/ml) at index date ***	500 (50-18859.5)	153 (50-3700)
≤50	59 (36)	362 (44.4)
]50,500]	29 (17.7)	145 (17.8)
]500,5000]	22 (13.4)	118 (14.5)
>5000	54 (32.9)	191 (23.4)
ARV treated before index date*	158 (96.3)	727 (89.1)
Year of treatment before index date*	1995 (1993-1997)	1997 (1997-1999)
Cumulated years of ARV treatment		
ARV	7.25 (4.45-10.69)	4.36 (1.59-7.16)
IP	3.41 (1.40-6.22)	0.80 (0.00-2.93)
NRTI	7.25 (4.36-10.48)	4.29 (1.47-6.97)
NNRTI	0.85 (0.00-2.21)	0.00 (0.00-1.95)
Others	0.00 (0.00-0.00)	0.00 (0.00-0.00)

Results are expressed as median (Q1-Q3) or n(%)
*** Index date : anal cancer date**
****pVL : plasma HIV RNA**

Table 2. Conditional logistic regression for anal risk cancer

	Univariable OR (95% CI)	Multivariable 1 OR (95% CI)	Multivariable 2 OR (95% CI)	Multivariable 3 OR (95% CI)	Multivariable 4 OR (95% CI)
Geographic Origin					
France	1	1	1	1	1
Sub-Saharan Africa	0.36 (0.10,1.25)	0.34 (0.09,1.28)	0.33 (0.09,1.22)	0.53 (0.12,2.29)	0.57 (0.14,3.28)
Other	0.93 (0.40,2.16)	0.70 (0.28,1.77)	0.71 (0.28,1.82)	0.65 (0.23,1.85)	0.63 (0.22,1.84)
AIDS stage					
No	1	1	1	1	1
Yes	2.26 (1.50,3.38)	1.84 (1.16,2.92)	1.31 (0.80,2.15)	2.03 (1.20,3.44)	1.56 (0.89,2.73)
Hepatitis B antigen +					
No	1	1	1	1	1
Yes	1.97 (1.15,3.35)	1.86 (1.01,3.44)	1.86 (0.99,3.48)	1.42 (0.69,2.94)	1.44 (0.69,2.99)
Hepatitis C antibodies +					
No	1	1	1	1	1
Yes	0.71 (0.39,1.27)	0.88 (0.46,1.67)	0.88 (0.46,1.67)	0.79 (0.38,1.66)	0.78 (0.38,1.63)
CD4 cell count (/mm³) nadir * by 100	0.62 (0.54,0.70)		0.75 (0.65,0.86)		0.77 (0.65,0.91)
pVL(copies/ml) at index date in log10**	1.23 (1.07,1.41)	1.40 (1.18,1.66)	1.41 (1.18,1.67)	1.45 (1.19,1.77)	1.45 (1.19,1.78)
Cumulated years of ARV treatment					
PI	1.47 (1.35,1.60)	1.52 (1.37,1.68)	1.43 (1.29,1.58)	1.15 (1.03,1.29)	1.09 (0.97,1.22)
NNRTI	1.05 (0.96,1.15)	1.19 (1.05,1.35)	1.18 (1.03,1.34)	0.96 (0.83,1.11)	0.95 (0.82,1.09)
NRTI	2.16 (1.85,2.53)			1.98 (1.67,2.34)	1.92 (1.63,2.26)
Others	10.20 (2.66,39.13)	1.95 (0.69,5.50)	1.93 (0.69,5.41)	2.77 (0.73,10.53)	2.80 (0.86,9.07)

***At treatment before index date or index date if not treated**
****pVL :plasma HIV RNA**

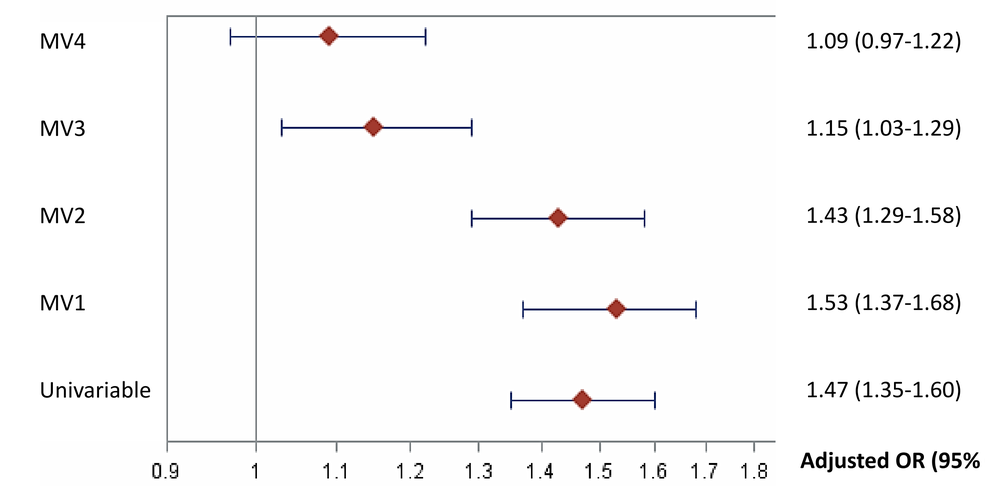
Figure 2. Risk of anal cancer according to cumulated years of PI use.

Multivariable 4 (MV4): MV1 + adjustment for NRTI and CD4 nadir

Multivariable 3 (MV3): MV1 + adjustment for NRTI

Multivariable 2 (MV2): MV1 + adjustment for CD4 nadir

Multivariable 1 (MV1) : not adjusted for CD4 nadir nor NRTI



Conclusions

- Our study analysed the risk of anal cancer in PLWH according to cumulated duration of ARV use.
- We found that the effect size associated with PI use
  - was significantly associated with the risk of anal cancer in univariable analysis
  - but when adjusting for NRTI, it was reduced and was no longer significant when further adjustment for the CD4 nadir was added.
- Our study shows the importance of taking into account complete ARV exposure as well as the immune depression history of PLHIV when evaluating the risk of developing an anal cancer.

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