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High-risk HPV genotypes are only associated with anal cytologic abnormalities but not with malignant histological lesions in a cohort of people living with HIV (PWH)

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Introduction/Summary

- The risk of cytological abnormalities in people living with HIV (PWH) is higher than in general population.
- The last guidelines of International Anal Neoplasia Society updated to 2023 (1) recommend to screen Men who have sex with Men (MSM) and Transgender Women with HIV since 35 yo and Men who have sex with Women (MSW) and Women (W) since 45 yo.
- HPV testing is considerend expecially in Atipical Squamous Cells of undetermined significance (ASCUS) and in Low Grade Squamous Intrahepitial Lesion (LSIL) results to decide to proceed to High Resolution Anoscopy (HRA).
- Our aim was to describe a long-term follow up of PWH that were screened for cytological abnormalities (CA) and HPV genotypes in anal swabs and find possible association between the occurrence of CA/histological abnormalities and patient characteristics.

Study Design/Methods

- A retrospective analysis of data collected from clinical practise.
- Screening for anal cancer (cytological exam and HPV detection in anal swabs) were offered to all PWH of our center since March 2010. All PWH were recommended to perform HRA. If CA were found. If HRA showed any abnormalities a histological exam was performed.
- The following HPV genotypes (other than 16 and 18) were defined as high risk HPV (HR-HPV) genotypes: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59. Classes of antiretroviral therapy (ART) were defined as non-nucleoside transcriptase inhibitors, protease inhibitors and integrase strand transfer inhibitors.

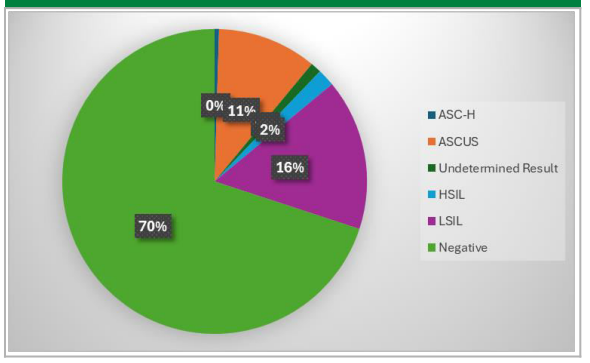
Results 1-(Cytologic)

- Characteristics of PWH enrolled in the study were showed in Table 1.
- Prevalences of CA were depicted in Figure 1.
- The following variables were associated with CA vs normal cytology: positivity for HPV 16 or/and 18 (65/126, 51% vs 71/310, 22.9%; p<0.001), positivity for any other HR-HPV (102/126 [81%] vs 163/310 [52.6%]; p<0.001), previous sexually transmitted Infections (STI) (88/126 [69.8%] vs 138/310 [44.5%]; p<0.001), duration of infection (median 9.42 [Interquartile range, IQR 3.37-18.20] vs 6.92 [2.87-14.97]; p<0.05).

Table 1 Characteristics of enrolled PWH

Variables	Median (IQR) or N (%) N=436
Age, years	45 [38;52]
Gender (male)	369 (84.6)
MSM	226 (51.8)
MSW	73 (16.7)
W	67 (15.4%)
IVDU	24 (5.5)
Previous AIDS diagnosis	107 (24.5)
CD4 cell count, cell/mm^3	659 [465;829]
HIV-RNA detectable	89 (21.8)
STI prevalence	226 (51.8)
Current c-ART	
NNRTI use	166 (41.5)
INSTI use	137 (34.2)
PI use	123 (30.8)
Previous c-ART (months)	
NNRTI use	6.84 [0;50.73]
INSTI use	0 [0;15.50]
PI use	3.97 [0;48.40]
Median number of cytogical exams	2 [1;3]
Negative citology	310 (71.1)
HSIL	8 (1.8)
LSIL	70 (16.1)
ASCUS	46 (10.6)
HPV prevalence total	365 (83.7)
HPV prevalence (MSM)	205/226 (90.7)
HPV prevalence (MSW)	60/73 (82.2)
HPV prevalene (W)	48/67 (71.6)
HPV vaccination (%)	119 (27.3)

Figure 1 **Prevalence of cytologic abnormalities**



Legend to the table: MSM Men who have sex with men, MSW Men who have sex with Women, W, Women, IVDU, Intravenous Drug Users, STI, Sexually transmitted Infections;. ART Antiretroviral Treatment; PI Protease Inhibitors, NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor, NRTI, Nucleoside reverse transcriptase inhibitors, INSTI Integrase strand transfer inhibitors HSIL, High grade Squamous Intrahepitelial Lesions ; ASC-H, Atypical Squamous Cells, Cannot Rule Out High Grade Squamous Intra-epithelial Lesion; LSIL, Low Grade Squamous Intrahepitial Lesion, ASCUS Atypical Squamous Cells of Undetermined Significance.

Results 2-(Cytologic)

- Prevalence of CA was not significantly different in MSM vs MSW and vs W (78/226 [34.5%] vs 16/73 [21.9%] vs 13/54 [24.1%], respectively; p=0.081). No association was found with age, CD4 nadir, current CD4, HIV-RNA, duration of ART, current or previous exposure to different classes of ART, and HPV vaccination.
- .Comparing ASC-H/HSIL vs ASCUS/LSIL, an association with a longer duration of antiretroviral treatment (ART) was also found: 15.79 (8.62-17.25) vs 6.04 (2.17-13.78) years, respectively; p=0.018.

Results (HRA)

- 79 PWH had at least one histological evaluation. 44/79 (55.7%) had a negative HRA, 15/79 (18.9%) had benign lesions, 20/79 (25.3%) showed malignant lesions: eleven anal intraepithelial neoplasia (AIN)-1, four AIN-2, four AIN-3 and one squamous cell carcinoma.
- 39/79 (49.4%) PWH performed HRA one time; , 11/79 (13.9%) 2 times, 29/79 (36.7%) ≥3 times (up to 6 times).
- The association with clinical variables and HRA results are depicted in table 2.

Conclusions

- CA are associated with HPV 16 and/or 18, other HR-HPV , previous STI and duration of infection. Malignant histological lesions are only associated with a previous STI.
- PI exposure is associated with negative HRA. A possible anticancer-role of Pis has been described in literature (2) even If, on the other hand, an association with anal cancer was demonstrated in DAD cohort (3).

Table 2 Results of High Resolution Anoscopy and clinical , immunologic and virological variables

Variables	Level	Negative HRA N=44	BL N=15	ML N=20	p
Cytologic results (%)	HSIL_ASC-H LSIL_ASCUS Negative	4 (9.1) 36 (81.8) 4 (9.1)	1 (6.7) 11 (73.3) 3 (20.0)	3 (15.0) 17 (85.0) 0 (0.0)	0.317
HPV_16_18 (%)	No Yes	26 (59.1) 18 (40.9)	7 (46.7) 8 (53.3)	6 (30.0) 14 (70.0)	0.095
STI (%)	No Yes	20 (45.5) 24 (54.5)	0 (0.0) 15 (100.0)	4 (20.0) 16 (80.0)	**0.002**
Sex (%)	F M	6 (13.6) 38 (86.4)	1 (6.7) 14 (93.3)	0 (0.0) 20 (100.0)	0.194
Years with HIV (median [IQR])		9.69 [4.27, 19.48]	5.57 [1.13, 17.14]	9.29 [4.88, 17.54]	0.452
Years on ART (median [IQR])		9.08 [2.85, 16.59]	3.17 [1.01, 9.82]	8.28 [5.14, 14.39]	0.059
CD4 cell count (median [IQR])		672 [442, 808]	773 [582.75, 896.50]	692.50 [481.75, 886.75]	0.310
HIVRNA (%)	<20 copies/ml >20 copies/ml	37 (84.1) 7 (15.9)	11 (78.6) 3 (21.4)	14 (77.8) 4 (22.2)	0.802
PI_EXP (median [IQR])		18.13 [0.00, 85.54]	0.00 [0.00, 0.00]	0.00 [0.00, 31.43]	**0.014**
NNRTI_EXP (median [IQR])		11.90 [0.00, 55.43]	13.57 [0.00, 82.36]	37.41 [8.89, 69.59]	0.488
INSTI_EXP (median [IQR])		0.00 [0.00, 23.38]	0.00 [0.00, 10.72]	0.00 [0.00, 0.61]	0.194

Legend to the table: HRA, High Resolution Anoscopy; BL, Benign Lesions; ML Malignant Lesions, HSIL, High grade Squamous Intrahepitelial Lesions ; ASC-H, Atypical Squamous Cells, Cannot Rule Out High Grade Squamous Intra-epithelial Lesion; LSIL, Low Grade Squamous Intrahepitial Lesion, ASCUS Atypical Squamous Cells of Undetermined Significance; STI, Sexually transmitted Infections; ART Antiretroviral Treatment; EXP, exposure; PI Protease Inhibitors, NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor, NRTI, Nucleoside reverse transcriptase inhibitors, INSTI Integrase strand transfer inhibitors.

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