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HPV-mediated cytological abnormalities and high-risk HPV genotypes associate with altered gut microbiota composition and function in cART-treated HIV+ males

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Background

HIV infected individuals feature higher incidence of HPV persistence at both vaginal and anal level.

Recently, the gut microbiota has been demonstrated to predict precancerous anal lesions, suggesting that some taxa featuring HIV-associated dysbiosis might fuel HPV persistence and pathogenesis.

Aim

To explore whether the presence of HPV-related cytological abnormalities might be associated with bacteria functional modifications and with HIV-mediated gut mucosal dysfunction (i.e. increased gut permeability, microbial translocation MT and consequent immune activation IA) within the anal district of cART-treated HIV+ males.

Methods

Patients

- ✓ HIV+ males on suppressive cART (HIV-RNA<40cp/ml) and asymptomatic for STD were enrolled at the Clinic of Infectious Diseases, Dept of Health Sciences, ASST Santi Paolo e Carlo, University of Milan.

Specimen collection

- ✓ Anal swab, blood, stool

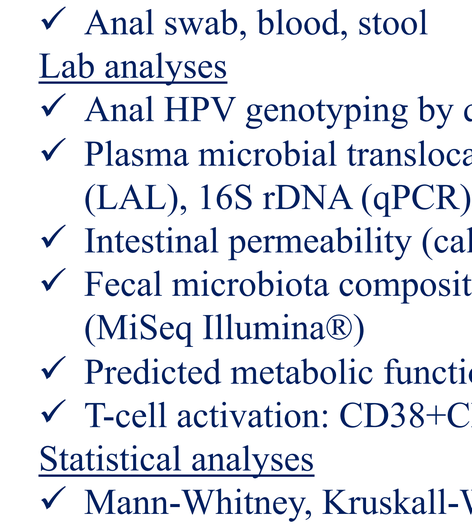
Lab analyses

- ✓ Anal HPV genotyping by qPCR and sequencing analysis
- ✓ Plasma microbial translocation (MT) markers: sCD14 (ELISA), LPS (LAL), 16S rDNA (qPCR)
- ✓ Intestinal permeability (calprotectin, I-FABP)
- ✓ Fecal microbiota composition: relative abundance, α- and β-diversity (MiSeq Illumina®)
- ✓ Predicted metabolic function (PICRUSt)
- ✓ T-cell activation: CD38+CD8+ and CD45R0+CD38+CD8+

Statistical analyses

- ✓ Mann-Whitney, Kruskall-Wallis. Chi-squared tests

Results I: characteristics of the study population



*Normal cytology: absence of cytological abnormalities
°Altered cytology: presence of ASCUS, LSIL, HSIL.

	HPV negative (n=6)	HPV positive (n=30) Normal cytology (n=12)	HPV positive (n=30) Altered cytology (n=18)	p
Age, years (IQR)*	52 (45-61)	38 (32-60)	51 (37.5-57)	0.304
Risk Factors, (%)°				0.169
Heterosex	1 (17)	2 (17)	1 (6)	
Homosex/Bisex	4 (66)	10 (83)	17 (94)	
IDU	1 (17)	0 (0)	0 (0)	
HCV/HBV co-infection, (%)*				0.038
Yes	2 (33)	1 (8)	0 (0)	
Monocytes, % (IQR)*	8.15 (6.07-10.48)	7.75 (6.9-9.2)	7.60 (6.80-9.87)	0.967
Limphocytes, n (IQR)*	1931 (1498-2250)	1843 (1498-2394)	2054 (1920-2550)	0.136
CD8 T-cell count, cell/mmc (IQR)*	813 (718-1234)	821 (727-994)	833 (778-1028)	0.865
CD4 T-cell count, cell/mmc (IQR)*				
Nadir	271 (91-398)	294 (148-414)	365 (280-544)	0.201
At time of analysis	465 (366-512)	702 (457-983)	706 (635-839)	0.013
CD4/CD8 ratio, (IQR)*	0.49 (0.32-0.72)	0.74 (0.58-0.99)	0.78 (0.66-1.08)	0.042
AIDS diagnosis° (%), (yes)	0 (0)	2 (17)	3 (17)	0.599
Time since First HIV Ab+, years (IQR)*	6 (5.5-12)	7.5 (5.2-11.5)	6.5 (5-10)	0.615
HIV-RNA Zenith Log cp/mL (IQR)*	4.8 (4-5.92)	4.74 (4.55-5.10)	5.31 (4.66-5.79)	0.499
HIV-RNA cp/mL (IQR)* at time of analysis	0 (0-10)	0 (0-30)	0 (0-10)	0.925
cART duration, years (IQR)*	6 (5-7)	5 (5-8)	4.5 (4-5)	0.032
cART regimen (%)°				0.602
NRTIs+PI/r	1	2	4 (22)	
NRTIs+NNRTI	3	7	8 (44)	
Others	2	3	6 (34)	

Note: *data are presented as median IQR, Kruskall-Wallis test; °data are presented as numbers (%), Chi-squared; IQR: interquartile range; IDU: intravenous drug user, cART: combination antiretroviral therapy; NRTIs: nucleoside reverse transcriptase inhibitors, Pis: protease inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors

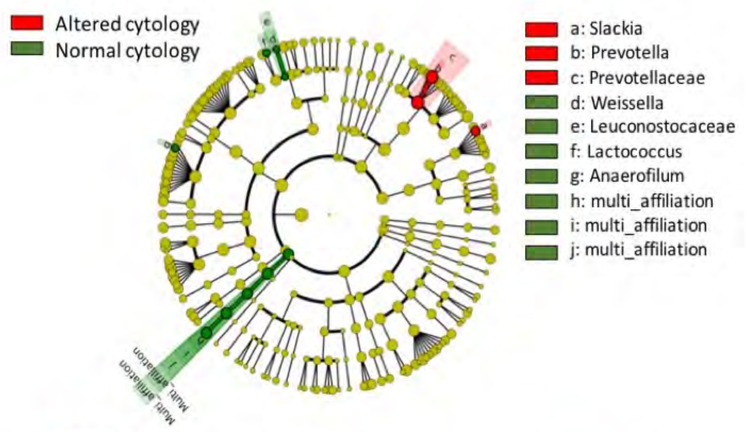
Results II: immune activation, microbial translocation and intestinal permeability

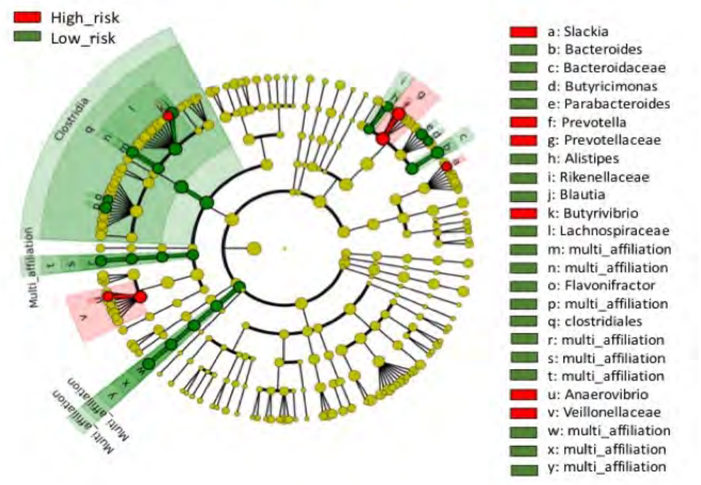
We failed to detect any difference in markers of intestinal permeability, MT and IA among the study groups

Results III:

a. aHPV patients showed a marked dysbiosis, with higher proportion of *Prevotellaceae* and lower *Leuconostocaceae*

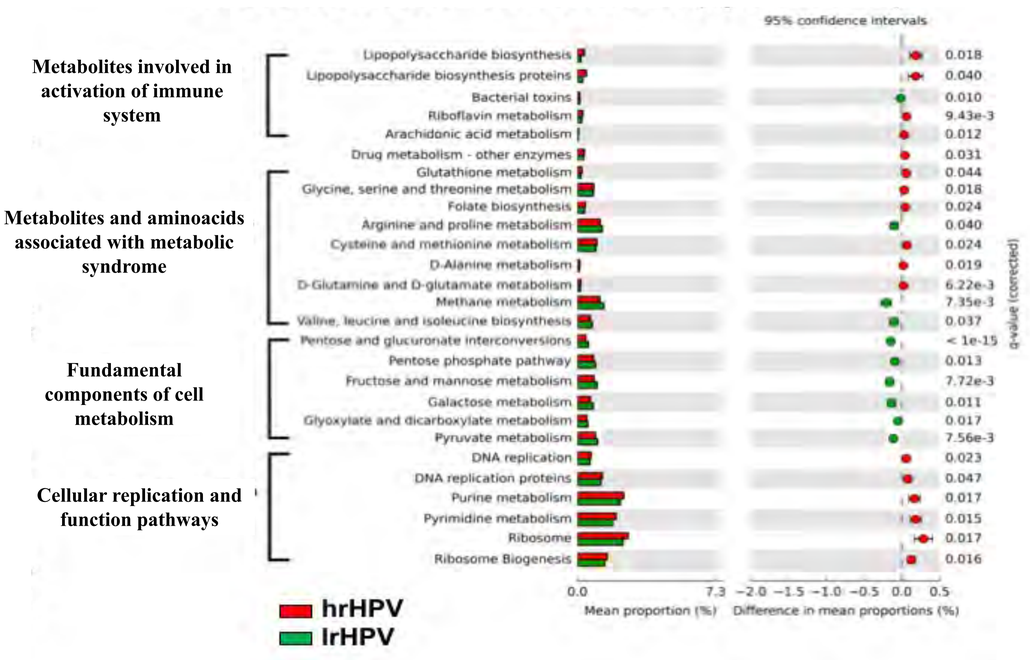
b. the presence of high-risk HPV genotypes, irrespective of cytological abnormalities, seemed to have a greater impact on gut dysbiosis, with hrHPV displaying higher proportion of *Prevotellaceae* and *Veillonellaceae*, but lower *Bacteroidaceae, Lachnospiraceae* and *Rikenellaceae* as compared to lrHPV





Results IV: predicted metabolic function

HIV+ patients with HPV-mediated cytological abnormalities and/or high-risk HPV genotypes showed increased abundance of genes related to immune system activation and to metabolic syndrome



Discussion

- The presence of HPV-related cytological abnormalities within the anal district is characterized by unique bacteria composition and functional metagenomic capacity, supporting a pathogenic link between gut microbiota and HPV.
- From a clinical standpoint, the observations of a *Prevotellaceae*-rich/*Bacteroidaceae*-poor profile, coupled with changes in metabolites involved in sustaining immune activation and co-morbidities seem to support the establishment of a pro-inflammatory environment that favors high-risk HPV genotype persistence and HPV-mediated cytological abnormalities.

References:
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