P17 & FP – **HPV-mediated cytological abnormalities and high-risk HPV genotypes associate with altered gut microbiota composition and function in cart-treated HIV+ males**

E. Merlini[1], C. Tincati[1], A. Pandolfo[1,2], B. Cassani[3], F. Bai[1], G. Ancona[1], A. Barassi[4], G. Bulfamante[3], A. d'Arminio Monforte[1], G. Marchetti[1]

[1]*Clinic of Infectious Diseases, Dept of Health Sciences, University of Milan, ASST Santi Paolo e Carlo, Milan, Italy.*

[2]*Clinic of Infectious Diseases, ASST Lecco, Italy.*

[3]*Pathology Unit, Dept of Health Sciences, University of Milan, ASST Santi Paolo e Carlo, Milan, Italy.*

[4]*Biochemistry Laboratory, Dept of Health Sciences, University of Milan, ASST Santi Paolo e Carlo, Milan, Italy.*

esther.merlini@gmail.com

Background: HIV-infected individuals feature higher incidence of HPV persistence at both vaginal and anal level (1,2). Recently, the gut microbiota has been demonstrated to predict precancerous anal lesions (3), suggesting that some taxa featuring HIV-associated dysbiosis might fuel HPV persistence and pathogenesis.

Objective: We decided 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.

Methodology: We enrolled 36 HIV+ males on cART (HIV-RNA<40cp/ml) and collected anal swab, blood and stool samples.

Normal cytology: absence of cytological abnormalities; altered cytology: presence of ASCUS, LSIL, HSIL. Lab analyses: (i) anal HPV genotyping and cytological evaluation; (ii) fecal microbiota composition (relative abundance, α-/β-diversity); (iii) bacterial metagenome prediction (PICRUSt); (iv) intestinal permeability (Calprotectin, I-FABP); (v) MT (sCD14, LPS, 16S rDNA); (vi) T-cell activation (CD8+CD38, CD8+CD38+CD45R0+). Mann-Whitney, with Bonferroni's correction and Chi-squared tests were used.

Results: We identified 30/36 (83%) HPV+ patients, 24/30 harboring high-risk HPV genotypes (hrHPV). Of these, 18 had HPV-related cytological abnormalities w/o neoplasia (aHPV, Fig.1a).

aHPV patients showed a marked dysbiosis, with higher proportion of Prevotellaceae and lower Leuconostocaceae (Fig.1b). Interestingly, 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 (Fig.1c).

This shift in bacterial composition was accompanied by changes in predicted metabolic capacity (Fig.1d). Indeed, 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.

While the presence of HPV-mediated cytological abnormalities and high-risk HPV genotypes associates with gut dysbiosis, we failed to detect any difference in markers of intestinal permeability, MT and IA.

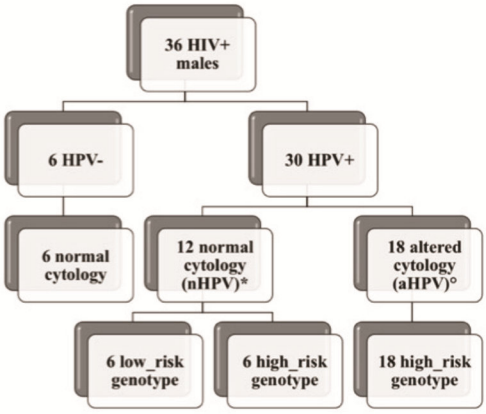
Conclusions: In cART-treated HIV+ males, the presence of HPV-related cytological abnormalities within the anal district is characterized by unique bacteria composition and functional metagenomic capacity, supporting a pathogenic link between gut microbiota and HPV. From a clinical standpoint, the observations of a Prevotellaceaerich/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

1. Marchetti G et al, J Sex Transm Dis, 2013
2. Thorsteinsson K et al, J Clin Virol, 2018
3. Serrano-Villar S et al, AIDS, 2017

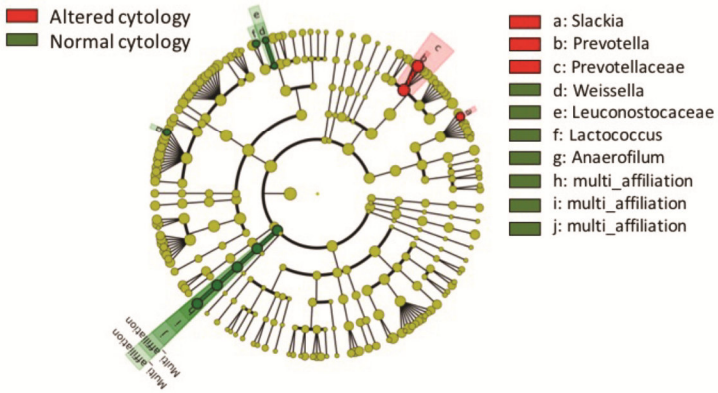
Figure 1

a. Diagram illustrating the study population

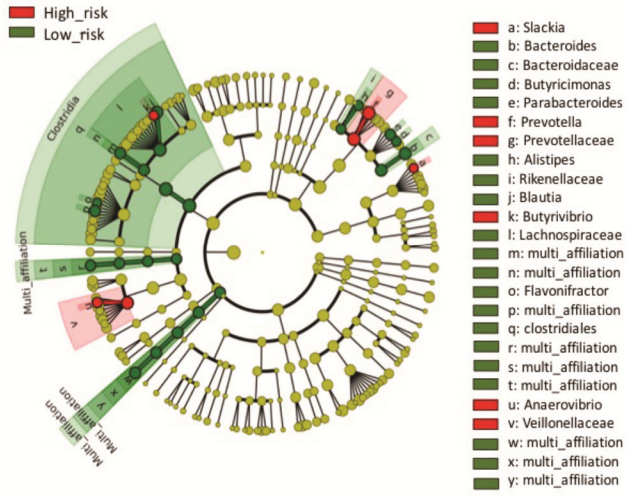


*Normal cytology: absence of cytological abnormalities
°Altered cytology: presence of ASCUS, LSIL, HSIL.

b. LEfSe analyses_anal cytology



c. LEfSe analyses_high-risk HPV genotypes



d. Predicted metabolic function (by PICRUSt)