Matteo Augello, M.D.
Clinic of Infectious Diseases
and Tropical Medicine,
Department of Health Sciences,
University of Milan

UNIVERSITÀ
DEGLI STUDI
DI MILANO

Treponema pallidum coinfection in HPV-related anal/cervical dysplasia progression in PLWH

Background

- HPV-related dysplasia is a **precursor** of anal and cervical cancer.
- HIV-infected subjects are at increased risk of HPV-related disease **progression** and cancer development:

- higher HPV/high-risk genotypes prevalence;
- immune-depression/impaired T-cell homeostasis;
- impairment of HPV-specific immunity.

- Understanding which factors are associated with an increased risk of Squamous Intraepithelial Lesions (SIL) progression is necessary for the development of HPV-related cancer prevention strategies in HIV-infected subjects.

Leng et al. HIV Med 2017; Rovelli et al. *Plos One,* 2017
Tincati et al. CID 2016; Tong et al. *JID,* 2015
Robbins et al. *J Natl Cancer Inst,* 2015
Mendez-Martinez et al. *BMC Infect Dis*, 2014

Aim of the study

We aimed to investigate the **demographic and immunological factors associated with the progression** of anal/cervical squamous intraepithelial lesions (SIL) in a cohort of HIV-infected subjects.

Materials and methods (I)

- **Retrospective study** at the Clinic of Infectious Diseases and Tropical Medicine, San Paolo Hospital, Milan.
- **Male and female HIV-positive patients** who underwent, in the period 01/2006-11/2019 (N=398):
- **anal/cervical PAP smears**: Atypical Squamous Cells of Undetermined Significance (ASCUS), Low-grade SIL (LSIL), High-grade SIL (HSIL);
- **HPV genotyping**: High Risk (HR) and Low Risk (LR) genotypes.
- Patients repeated PAP smears every 8-12 months depending on the clinical indication.
- Patients were followed up from the enrollment in the cohort (i.e. the first surgical/gynecological examination with PAP smears) to the last available examination/lost to FU.

Materials and methods (II)

- Inclusion of the following parameters at the time of the **first cytological evaluation**:

- demographic: age, sex, smoke, co-infections (HCV, HBV, syphilis);
- HIV-related: epidemiology, nadir/current CD4+, AIDS, type of cART, naïve/treated; HIV-RNA;
- HPV-related: negative, LR, HR;
- Immune: CD4+, CD8+, CD4+/CD8+ T-cell ratio; CD8+CD38+; CD8+CD38+45RO+; CD4+ and CD8+ CD127-expressing cells.

- **SIL progression** defined as development of a higher grade of HPV-related dysplasia.
- **SIL stable/regression** defined as stability/development of lower grade of HPV-related dysplasia.
- Chi-squared/Mann-Whitney test, Kaplan Meier survival analysis with log-rank test and Cox proportional hazards regression analysis were used for statistics.

SIL progressors are more commonly males, co-infected with HCV and *T. pallidum*

Parameter	Study population (N=398)	SIL stable/regression (N=302)	SIL progression (N=96)	*p*-value
Males, n (%)°	291 (73%)	211 (70%)	80 (83%)	**0.01**
Mode of HIV transmission, n (%)				0.354
Homosexual contact	237 (59.5%)	173 (57.3%)	64 (66.7%)	
Heterosexual contact	111 (27.9%)	90 (29.8%)	21 (21.9%)	
IDU	31 (7.8%)	26 (8.6%)	5 (5.2%)	
Other	10 (2.5%)	7 (2.3%)	3 (3.1%)	
Unknown	9 (2.3%)	6 (2%)	3 (3.1%)	
HCV coinfection, n (%)				**0.02**
HCV-Ab negative	337 (84.7%)	259 (85.8%)	78 (81.3%)	
HCV-Ab pos HCVRNA neg	46 (11.6%)	30 (9.9%)	16 (16.7%)	
HCV-Ab pos HCVRNA pos	12 (3%)	12 (4%)	0	
Unknown	3 (0.8%)	1 (0.3%)	2 (2.1%)	
HBV coinfection, n (%)				0.42
Negative or vaccinated	280 (70.4%)	218 (72.2%)	62 (64.6%)	
HBsAg positive	11 (2.8%)	9 (3%)	2 (2.1%)	
HBcAb positive	101 (25.4%)	71 (23.5%)	30 (31.3%)	
Unknown	6 (1.5%)	4 (1.3%)	2 (2.1%)	
Syphilis coinfection, n (%)				**0.04**
TPPA neg	232 (58.3%)	186 (61.6%)	46 (47.9%)	
TPPA pos	140 (35.2%)	96 (31.8%)	44 (45.8%)	
Unknown	26 (6.5%)	20 (6.6%)	6 (6.3%)	
Smoke, n (%)				0.87
No	172 (43.2%)	128 (42.4%)	44 (45.8%)	
Yes	198 (49.7%)	153 (50.7%)	45 (46.9%)	
Ex-smoker	6 (1.5%)	4 (1.3%)	2(2.1%)	
Unknown	22 (5.5%)	17 (5.6%)	5 (5.2%)	

No differences in HIV- and HPV-related parameters in SIL progressors and SIL non-progressors

Parameter	Study population (N=398)	SIL stable/regression (N=302)	SIL progression (N=96)	*p*-value
cART-treated **cART-naive**	307 (77.1%) 91 (22.9%)	235 (77.8%) 67 (22.2%)	72 (75%) 24 (25%)	0.567
Current cART regimen, n (%)				0.877
PI-based	108 (35.2%)	80 (34%)	28 (38.9%)	
NNRTI-based	122 (39.7%)	95 (40.5%)	27 (37.5%)	
INSTI-based	51 (16.6%)	39 (16.6%)	12 (16.7%)	
Other	26 (8.5%)	21 (8.9%)	5 (6.9%)	
Nadir CD4+ T cell count [cells/mmc], median (IQR)	300 (174-420)	286 (154-416)	325 (209-455)	0.141
Pre cART CD4/CD8 ratio, median (IQR)	0,38 (0.24-0.55)	0,38 (0.22-0.55)	0,37 (0.27-0.58)	0.222
Current CD4+ T cell count [cells/mmc], median (IQR)	529 (400-710)	528 (391-686)	556 (453-749)	0.172
Current CD8+ T cell count [cells/mmc], median (IQR)	879 (681-1171)	886 (684-1219)	860 (647-1045)	0.322
HIV-RNA, n (%)°				0.34
Detectable	126 (31.7%)	92 (30.6%)	34 (35.8%)	
Undetectable	270 (67.8%)	209 (69.4%)	61 (64.2%)	
Unknown	2 (0.5%)	1 (0.04)	1 (1.1%)	
HPV Infection, n (%)				0.178
Negative	87 (21.9%)	73 (24.2%)	14 (14.6%)	
LR genotype	51 (12.8%)	39 (12.9%)	12 (12.5%)	
HR genotype	248 (62.3%)	180 (59.6%)	68 (70.8%)	
Unknown	12 (3%)	10 (3.3%)	2 (2.1%)	

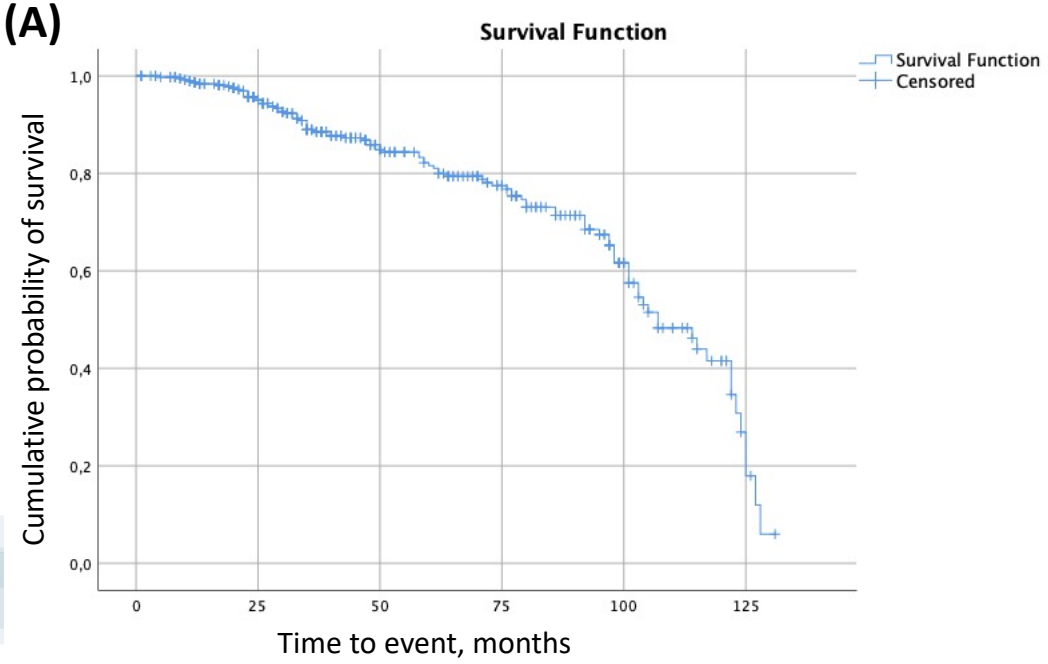
No differences in immune reconstitution and disease progression parameters in SIL progressors and SIL non-progressors

Parameter	Study population (N=398)	SIL stable/regression (N=302)	SIL progression (N=96)	*p*-value
Current CD4+CD127+ T cell count [cells/mmc], median (IQR)	329 (216-462)	325 (210-462)	337 (223-458)	0.985
Current CD8+CD127+ T cell count [cells/mmc], median (IQR)	406 (260-587)	408 (265-593)	400 (251-567)	0.464
Current CD8+CD38+ T cell count [cells/mmc], median (IQR)	60 (26-141)	56 (26-137)	76 (38-150)	0.089
Current CD8+CD3845RO+ T cell count [cells/mmc], median (IQR)	170 (22-205)	72 (20-199)	99 (30-240)	0.09
Current CD4/CD8 ratio, median (IQR)	0.61 (0.39-0.88)	0.6 (0.39-0.83)	0.64 (0.46-0.98)	0.062

Higher rate of SIL progression in *T. pallidum*-coinfected subjects

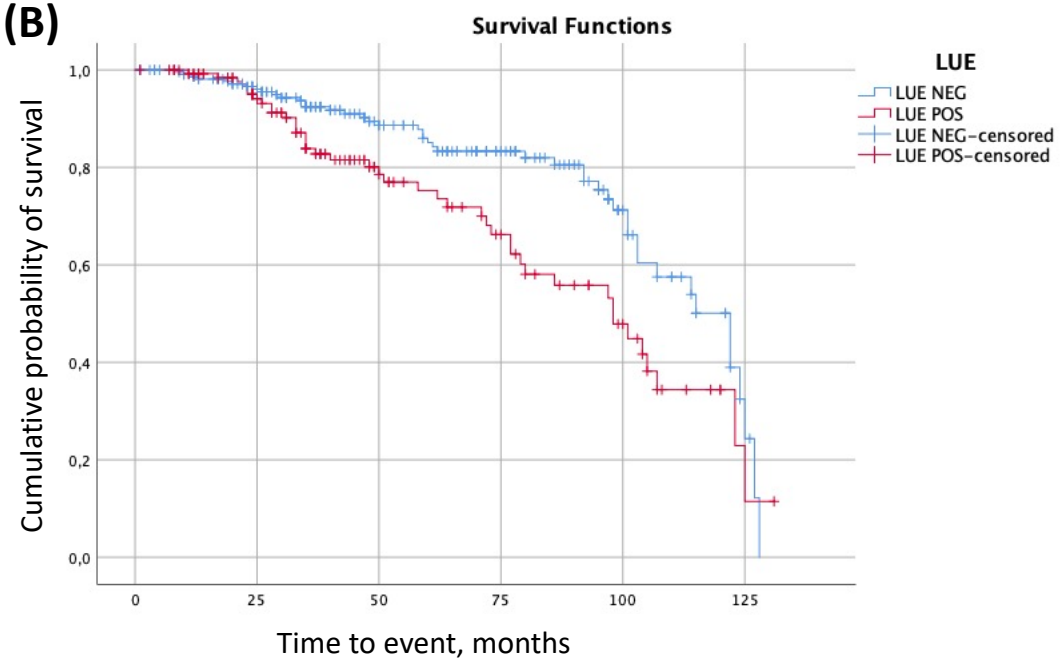
Kaplan-Meier estimates of probability of SIL progression in (A) the study population and (B) according syphilis co-infection

(A)



N	398	295	170	111	45	5

(B)



N	226	177	109	71	28	3
N	137	102	51	33	16	2

Overall mean survival time: 97.4 (CI95%, 92.67-102.18) months. 24- and 48-month probability of SIL progression: **5%** (CI95%, 3-7%) and **14%** (CI95%, 4-15%).

48-month probability of SIL progression: **9.8%** (CI95%, 4-15%) in syphilis-positive patients and **3.9%** (CI95%, 1-6.7%) in syphilis-negative subjects. **Log rank: *p*=0.006**.

Adjusted Cox Regression Model: syphilis associated with a trend toward a higher probability of SIL progression

Parameters	AHR	CI95%	*p*-value
Gender			
Female	1		
Male	1.449	0.705-2.977	0.312
HPV Infection			
Negative	1		0.723
LR HPV	0.788	0.33-1.884	0.593
HR HPV	1.038	0.528-2.042	0.914
Syphilis			
Negative	1		
Positive	**1.567**	**0.99-2.48**	**0.05**

Conclusions

- In the context of HIV-HPV coinfection:

- **syphilis was associated with SIL progression**, viro-immunological parameters were not;

- **exposure to HPV and other STDs are drivers of SIL pathogenesis in HIV-infected subjects rather than peripheral immune impairment**;

→ mirrors greater risk factors

→ underlying mechanism of disease?

- Management of HPV dysplasia in HIV disease should include:

- HPV vaccination,

- Prevention/treatment of syphilis infection.

Acknowledgments

Clinic and Laboratory of Infectious Diseases,

San Paolo Hospital,

Department of Health Sciences,

University of Milan

Camilla Tincati

Francesca Bai

Debora Mondatore

Esther Merlini (now Gilead Sciences)

Antonella d'Arminio Monforte

Giulia Marchetti

Our patients

Second Surgery Unit,
San Paolo Hospital,
Department of Health Sciences,
University of Milan
Andrea Pisani Ceretti
Marco Giovenzana
Enrico Opocher

Servicio de Enfermedades Infecciosas,
Hospital Universitario Ramón y Cajal,
Madrid
Sergio Serrano-Villar

Funding

Piano di Sostegno alla Ricerca, Università degli Studi di Milano, 2016

Eranet-Transcan2-Fondazione Regionale della Ricerca Biomedica (FRRB), 2016