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Evaluation of cell-mediated Immunity to HPV nonavalent vaccine (Gardasil9®) in a cohort of people living with HIV

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Background

HPV anorectal infection is the main cause of anal cancer in people living with HIV (PLWH); tetravalent vaccine has proven to elicit a sustained cell-mediate immunity (CMI) response[1] and to be effective in the primary[2] and secondary[3] prevention of HPV-related anal dysplasia. Data are lacking about the nonavalent HPV vaccine. Aim of our study is to assess the cell-mediate immunity in response to Gardasil9® vaccination in a cohort of PLWH.

Total Population	N= 20 patients
Sex (N, %)	
Male	19 (95%)
Female	1 (5%)
Age (years); median (IQR)	46,5 (39,25 – 51,5)
Ethnicity (N, %)	
Caucasian	19 (95%)
Hispanic	1 (5%)
Years of smoke; median (IQR)	22 (17 – 32,5)
HIV infection route (N, %)	
MSM	10 (50%)
Bisexual	2 (10%)
Heterosexual	2 (10%)
Not Available	6 (30%)
Years of HIV Infection; median (IQR)	8 (3,5 – 13,25)
CD4⁺ Nadir (cells/mmc); median (IQR)	368,5 (137 – 460,25)
Viremia Zenith (cp/ml); median (IQR)	96245 (25850 – 491000)
CDC stage (N, %)	
A1	5 (25%)
A2	5 (25%)
A3	2 (10%)
B3	1 (5%)
C3	3 (15%)
Not Available	4 (20%)
HIV subtype (N, %)	
A1	1 (5%)
B	13 (65%)
Recombinant	3 (15%)
Not available	3 (15%)
Years of ART; median (IQR)	7,5 (2,5 – 11,5)

Table 1. *General and HIV-related viro-immunolgical features of the study population at enrollment. CDC= Centers for Disease Control and Prevention; RAMs=Resistance-associated mutations; ART= Anti-Retroviral Therapy.*

Materials and Methods

We recruited PLWH in follow-up at the Infectious Diseases HIV Clinic of Policlinico Tor Vergata; Inclusion criteria were age ≥18 years, to be on antiretroviral therapy for at least 6 months and not being vaccinated for HPV. Gardasil9® was administered at baseline (T0), after 2 months (T2m) and 6 months (T6m). A final visit was performed 1 month after vaccine last dose (T7m). Blood samples were collected for viro-immunological follow-up and to assess CMI with IGRA test using peptide libraries for L1 (included in Gardasil9®) and E2 (not included in Gardasil9®) of HPV 16 and 18, dosing IFN-γ with an automated system (ELLA). Anorectal swabs were performed for HPV-DNA detection. Data are shown as median (IQR). Friedman test was used to compare medians and Spearman test was used to test correlation between quantitative variables.

Results

20 patients were enrolled, 19 were men (95%) with a median age of 47 years (39–52). Median years of HIV infection was 8 (4–13), with CD4 nadir of 369 cells/µl (137–460) and HIV-RNA zenith of 96245 cp/ml (25850–491000). Clinical characteristics are shown in **Table 1**. HPV anorectal infection at T0 with at least one high risk (HR) HPV genotype was detected in 16 out of 18 patients (89%), with a median number of HR genotypes of 2.5 (1–4), and a median of low risk (LR) genotypes of 1,5 (1–2,75). HPV16 was found in 5 patients (28%), while HPV18 was found in 2 patients (11%); HIV viro-immunological control was maintained in the entire population during the study period. CMI from T0 to T7m was assessed in a subset of 9 patients; T-cell response to L1 of HPV16 and 18 significantly increased from T0 to T7m ($p<0.001$, **Figure 1**). Conversely T-cell response to E2 of HPV16 and 18 did not show any significant increase over time. At T7m, L1 specific T-cell responses for HPV 16 and 18 showed a positive correlation with CD4+ nadir (Spearman rho: 0,8 p=0,06, and rho 0,9 p=0,02), and 4/9 patients obtained clearance of multiple HR HPV genotypes at T6m.

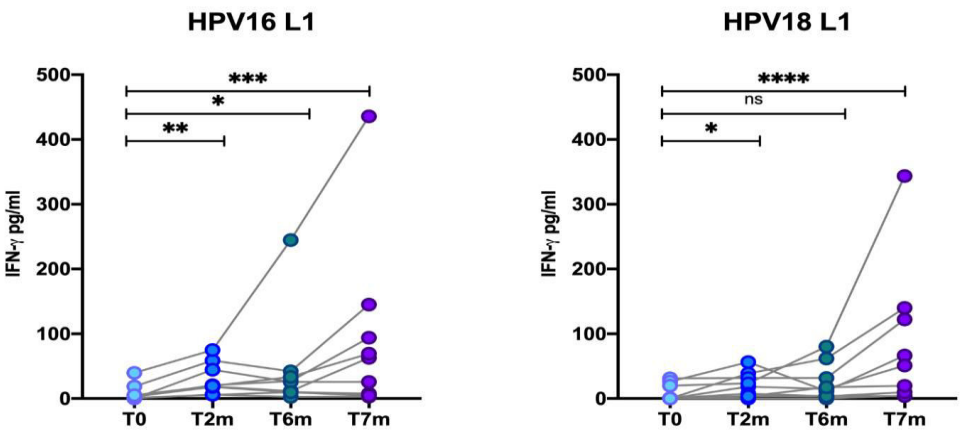

Figure 1. *Interferon-gamma (IFN-γ) production after stimulation with L1 peptide libraries of HPV16 and HPV18, from T0 to T7m in a subset of 9 PLWH. Statistical analysis was performed with the Friedman test for non-parametric data. Post hoc analysis was performed with the Dunn's test, with correction for multiple comparisons.*
** 0.01<p<0.05; ** 0.001<p<0.01; *** 0.001<p<0.0001; **** p<0.00001.*

Conclusions

PLWH with a low CD4+ may retain an "immunological scar" which prevent them to develop a full CMI against HR HPV. IGRA Test is a suitable screening tool to stratify this population in order to prevent HPV-related anal dysplasia and evaluate the potential benefit from a fourth dose of Gardasil9®[4].

References

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