Baseline CD4 Count Influences HPV Vaccine Response in People Living With HIV: Two-Year Follow-Up

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A baseline >500 CD4⁺ count is associated with stronger early cellular immune responses to HPV vaccination in PWH, with specific polyfunctional CD4⁺ and CD8⁺ increase.

BACKGROUND

HPV anorectal infection is the main cause of anal cancer in people living HIV (PWH).

Data on HPV-specific T-cell responses to the nonavalent vaccine in PWH are limited.

Given the critical role of cell-mediated immunity (CMI) in vaccine efficacy and in the control of the progression of dysplastic lesions and anti-tumor response, we evaluated **post-vaccination T-cell responses** in PWH on Anti-retroviral Therapy (ART), stratified by CD4 T-cell count at time of first vaccine dose and **up to two years after vaccination.**

METHODS

We prospectively enrolled PWH on ART. Inclusion criteria were age ≥18 years, undergoing ART for at least 6 months, and naïve to HPV vaccination. Nonavalent vaccine was administered at **baseline(T0), after 2 and 6 months(T1); follow-up continued to 6 months(T2) up to 2 years(T3)**.

We performed **anal swabs to search for HPV DNA**, and blood samples were collected for viro-immunological follow-up and to evaluate **CMI by flow cytometry** of CD4 and CD8 T cells producing IFN-γ, IL-2, or TNFα**(responding)** and all three cytokines **(polyfunctional)** after stimulation with a pool of HPV16 and 18 L1 peptides.

Adjusted linear mixed models with random intercepts and slopes for individuals and robust standard errors were used to estimate mean levels of CD4 and CD8 responding and polyfunctional cells comparing groups stratified by baseline CD4(>500 vs ≤500 cells/μL). Models were adjusted for age, sex, CD4 nadir, HIV viral load suppression and CD4 at baseline. Prior HPV infection was defined as the presence of at least one genotype detected by a swab, regardless of the district and documented by consulting all available clinical documentation collected prior to study.

RESULTS

A total of 38 patients were enrolled; clinical characteristics are shown in **Table 1.** Current T3 data were available for 27 patients out of 38 (71%). HIV viro-immunological control was maintained through T3, with 24 out of 27 patients with undetectable HIV viremia (89%), 6 of whom developed viremic blips during the follow-up, as shown in **Table 2**. At T3, anorectal infection with at least one high risk (HR) HPV genotype was detected in 19 out of 27 patients (70,4%), with a median number of HR genotypes of 2 (IQR 1–4), and a median of low risk (LR) genotypes of 1 (IQR 0–2). HPV16 infection was found in 5 patients (18,5%); Prevalences of HPV genotypes are shown in **Graph 1.**

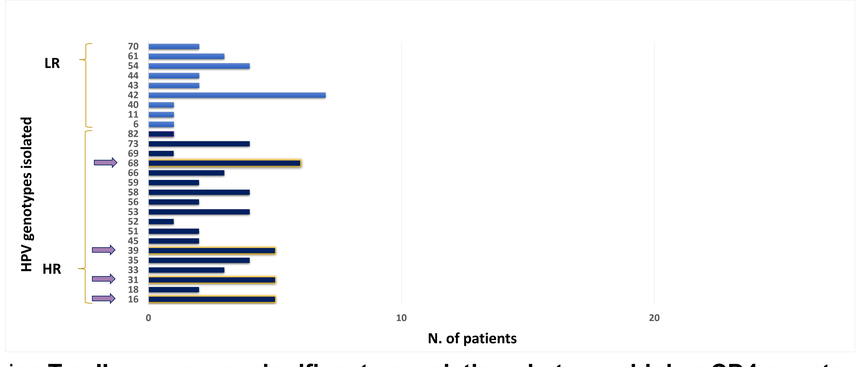
Table 1: Clinical and viroimmunological characteristics of the enrolled population at T0.

Total Population	N= 38 patients
Sex (N, %)	
Male	28 (74%)
Female	10 (26%)
Age (years); median (IQR)	42 (36 – 51,75)
Ethnicity (N, %)	
Caucasian	31 (82%)
Hispanic	3 (8%)
Asian	1 (2%)
African	3 (8%)
HIV infection route (N, %)	
MSM	23 (61%)
Bisexual	2 (5%)
Heterosexual	9 (24%)
PWID	2 (5%)
Congenital	2 (5%)
Years of HIV Infection; median (IQR)	8,5 (3,25 – 14,25)
CD4⁺ Nadir (cells/mmc); median (IQR)	314,5 (105,75 – 419,75)
CD4+ Baseline (cells/mmc); median (IQR)	679 (IQR 517.25–874)
CD4+ Count at baseline ≤ 500 cell/mmc (N, %)	8 (21%)
CD4+ Count at baseline > 500 cell/mmc (N, %)	30 (79%)
Viremia Zenith (cp/ml); median (IQR)	74080 (13743 – 173557)
Years of ART; median (IQR)	7 (IQR 2,5 – 11,5)

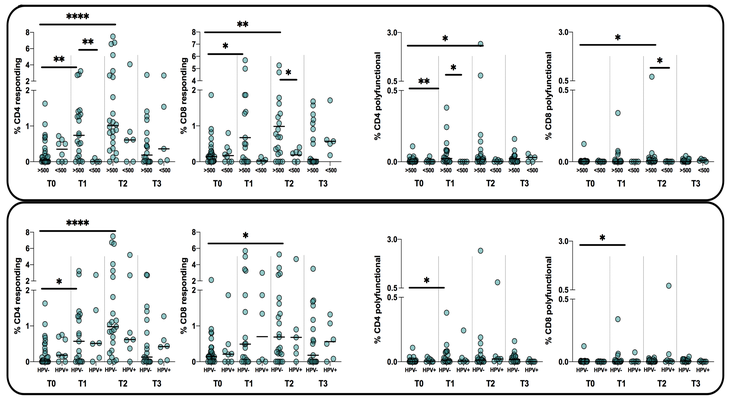
Table 2: Clinical and viroimmunological characteristics of the study population at T3

Total population	N= 27 patients
Days after completing the vaccination cycle; median (IQR)	737 (713 – 891,5)
Current CD4+ count (per mmc); median (IQR)	686 (478,5 – 938)
% CD4+ (per mmc); median (IQR)	34,9 (28,2 – 38,1)
Current CD8+ count (per mmc); median (IQR)	779 (458,5 – 1128,5)
% CD8+ (per mmc); median (IQR)	35,5 (28,5 – 45)
CD4+/CD8+ ratio; median (IQR)	0,98 (0,685 – 1,305)
Current CD19+ count (per mmc); median (IQR)	223 (167,5 – 265,5)
HIV-RNA PCR (cp/ml); median (IQR)	0 (0 – 0)
HIV viremia undetectable at T3 (N, %)	24 (89%)
New at-risk exposures(N; %)	19 (70,4%)
With a stable partner	9 (33%)
With multiple partners (>1)	10 (37%)
None	8 (30%)
HIV Viral blips in the observation period	
Patients who have had blips (N, %)	6 (22,2%)
Type of blip	
- Small	4 (66,6)
- Large	2 (33,3)
Other STDs diagnosed at T3 (N, %)	
Gonococcal Proctitis	3 (11,1%)

Graph 1: HPV genotype prevalences at T3



Concerning **T-cell responses, significant associations between higher CD4 counts and improved immune responses at earlier time-points were found.** Specifically, at T1, participants with >500 CD4 cells/μl showed significantly greater increases in CD4-responding (+1.19[95% CI: +0.28,+2.10],p=0.010), CD4-polyfunctional (+0.057[95% CI:+0.014, +0.100],p=0.009), and CD8-responding(+1.46 [95% CI:+0.65,+2.27],p=0.010) responses compared to those with ≤500 CD4 cells/μl. At T2, a significant difference persisted for CD8-responding cells(+2.32[95% CI:+0.51,+4.14],p=0.012).



*Statistical analysis was performed using Dunn's multiple comparison test, and a p-value <0.05 was considered significant. Statistical significance (p) is reported in the graphs. ****p < 0.0001; ***p < 0.001; **p < 0.01; *p < 0.05.*

By T3, most differences were no longer significant, except for CD8-polyfunctional cells, where a significant decrease was observed in the >500 CD4 group compared to the ≤500 group (Δ = –0.0044 [95% CI: –0.0208, –0.0049], p=0.001).

When stratifying the population by previous HPV infection, no significant differences emerged between the two subgroups.

CONCLUSIONS

In **PWH, baseline CD4 counts ≥500/mmc** are associated with **stronger early immune responses to HPV vaccination** with a significant **increase of CD4⁺ and CD8⁺ polyfunctional T cells** in comparison with PWH with <500 CD4⁺ .
Tailored vaccination schedules and follow-up may be warranted in PWH, particularly among them with lower CD4⁺ cells to ensure optimal and sustained protection. Future prospects aim to expand the sample of the population with <500 CD4 cells as well as the female population, which are poorly represented with current data.

ADDITIONAL KEY INFORMATION

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PLAIN LANGUAGE SUMMARY

In people living with HIV, better control of infection allows for a better cell-mediated response to HPV vaccination.