Viral Reservoir Dynamics after Therapeutic Vaccination and cART Interruption

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Goal

We present the results of a substudy of a dendritic cell based therapeutic vaccine. We assessed if the HIV-1 specific immune responses induced by the vaccine might have cleared some of the reservoir and drove the dynamics of replenisment of viral reservoir during cART interruption.

Introduction

We previously reported a peak decrease viral set-point of 1.2 log10 associated with an increase in HIV-1–specific T cell responses in HIV infected individuals receiving autologous myeloid derived dendritic cells (MDDC) pulsed with autologous heat-inactivated whole HIV.

Material and Methods

36 patients on cART were randomized to 3 immunizations with MDDC pulsed with HIV-1 (n=24) (cases) or with non-pulsed MDDCs (n=12) (controls). Virus for pulsing was isolated 56 weeks before the first immunization during a first cART interruption (STOP 1). Thereafter, cART was reinitiated and after 48 weeks 3 immunizations were performed and cART was interrupted again (STOP2). We measured total and integrated HIV-1 DNA in isolated CD4 T cells before any cART, before STOP1 (preSTOP1), before and after vaccination (VAC1 and VAC2) and at week 12 after second interruption of cART (STOP2). Data are expressed as mean $\log_{10}$ copies/10^6 CD4 T cells.

Results

•A drop in total and integrated DNA after the 3 years on cART from the precART period to the time point before STOP1 was observed
•Three months of cART interruption at STOP1 followed by 9 months of cART did not modify total and integrated DNA in these 36 subjects
•Vaccination (VAC1 to VAC2 period) did not influence DNA levels in vaccinated subjects
•After cART interruption post-vaccination (week 12), while total HIV-1 DNA significantly increased in both vaccinees (n=24) and controls (n=12), integrated HIV-1 DNA did not change in vaccinee and increased in controls (p=0.03 for the difference between groups).
•HIV-1 specific T cells responses at VAC2 time-point were strongly and inversely correlated with total and integrated HIV-1 DNA after vaccination (r= -0.46, p=0.04 and r= -0.79, p<0.0001, respectively) and after cART interruption in vaccinees (r= -0.69, p=0.002 and r= -0.82, p<0.0001, respectively), while a direct correlation was observed in DC-controls.
•These associations were mainly observed with HIV-1 specific T cell responses targeting gag p24 and p17 and nef antigens.

Figure 1. Clinical trial design

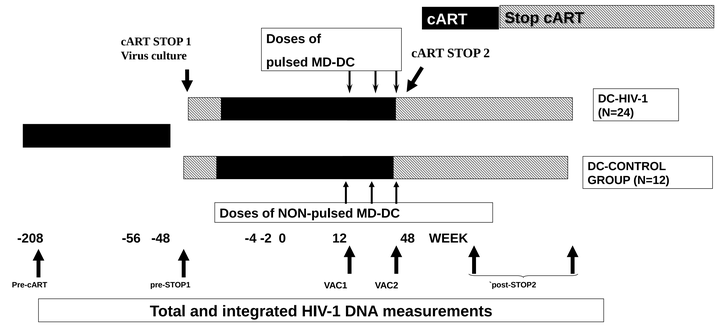
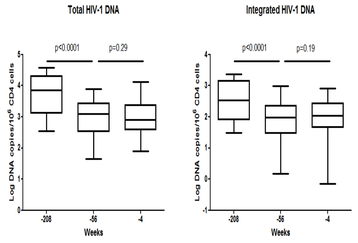


Table 1. Changes in total and integrated HIV-1 DNA after vaccinations in DC-HIV-1 and DC-Control groups.

Weeks	-208	-4	0	P"	12	P'	P"	48	P"	P'
Total HIV-1 DNA DC-HIV-1"	3.58 (0.19)	2.96 (0.11)	3.00 (0.10)	0.46	3.30 (0.11)	**0.0001**	**0.02**	3.48 (0.13)	**0.001**	0.76
Total HIV-1 DNA DC-Control"	3.99 (0.16)	3.07 (0.14)	3.12 (0.17)	0.43	3.59 (0.14)	**0.002**	0.50	3.68 (0.24)	**0.004**	0.20
Integrated HIV-1 DNA DC-HIV-1"	2.54 (0.20)	2.04 (0.14)	1.95 (0.15)	0.39	1.98 (0.17)	0.26	**0.01**	2.48 (0.11)	**0.002**	0.95
Integrated HIV-1 DNA DC-Control"	2.72 (0.20)	1.93 (0.15)	1.90 (0.13)	0.74	2.11 (0.13)	**0.02**	**0.03**	2.59 (0.16)	**0.01**	0.54

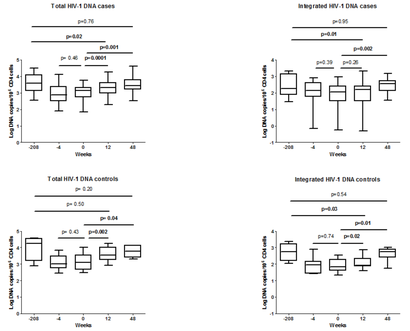
Week -208: before any cART; Week -4: day of the first immunization; Week 0: day of the interruption of cART and third immunization; Week 12 and 48: after cART interruption
[a]Mean (SE) $\log_{10}$ [b]P for the comparison between week -4 and 0 [c]P for the comparison between week 0 and 12; [d]P for the comparison between week -208 and week 12; [e]P for the comparison between week 0 and 48; [f]P for the comparison between week -208 and week 48

Figure 2. Changes in total and integrated HIV-1 DNA before vaccination



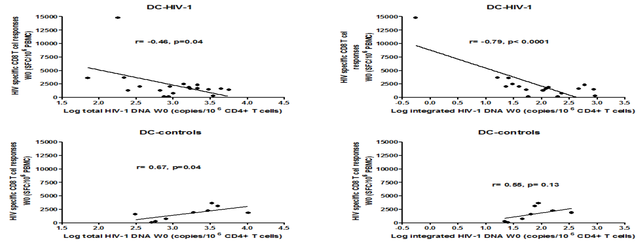
Week -208: before any cART; Week -56: before STOP1 (a first cART interruption 56 weeks before the first immunization to isolate virus for pulsing MDDCs); Week -4: day of the first immunization.

Figure 3. Changes in total and integrated HIV-1 DNA after vaccination and cART interruption



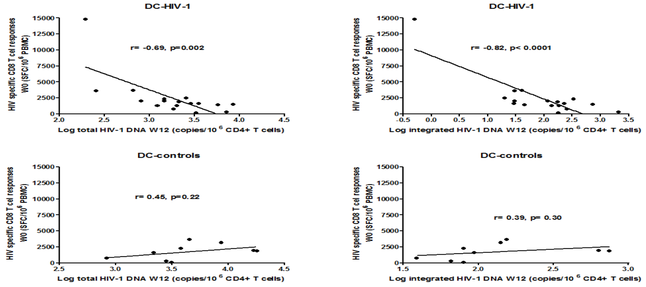
Week -208: before any cART; Week -4: day of the first immunization; Week 0: day of the interruption of cART and third immunization; Week 12 and 48: after cART interruption

Figure 4 Correlations between total and integrated HIV-1 DNA and total HIV specific T-cell immune responses of patients after vaccination and before cART interruption (week 0).



Magnitude of HIV-1 specific responses is defined as the sum of positive individual responses per patient. SFC/10^6 PBMC: spot forming cells/10^6 peripheral blood mononuclear cells. We observed that a single subject with extremely high ELISPOT values might have a strong influence on the linear regressions. Therefore, we considered this patient an outlier and repeated the analysis excluding this value. The association remained significant as follow: total HIV-1 DNA r= -0.46, p= 0.05; integrated HIV-1 DNA r= -0.53, p= 0.02.

Figure 5. Correlation between total and integrated HIV-1 DNA at week 12 after antiretroviral therapy interruption and total HIV specific T-cell immune responses of patients after vaccination and before cART interruption (week 0).



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Conclusion

HIV-1 specific T-cell immune responses elicited by therapeutic DC vaccines could drive changes in viral reservoir after vaccination and cART interruption in chronic HIV-1 infected patients treated at early stages.

Acknowledgements

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