VAC-3S, an Immunoprotective HIV Vaccine Directed to the 3S Motif of gp41, in Patients Receiving ART: Safety, Dose & Immunization Schedule Assessment.

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I ● Introduction and Background

We have developed a novel immunotherapeutic vaccine (VAC-3S), comprised of 3S peptide, a highly conserved HIV gp41motif coupled to commercially used carrier and adjuvant. The 3S motif leads, by NKp44L expression on CD4+ T cells (CD4), to apoptosis of uninfected CD4 (Figure 1 below). *In vitro*, anti-3S antibodies (Ab) protect CD4 from apoptosis. In cohort studies, anti-3S Ab correlate with lack of CD4 decrease and/or disease progression. VAC-3S primate proof-of-concept showed effect on immune and inflammatory biomarkers [*selected data shown below*]. Dose ranging studies, GLP toxicity and local tolerance studies were performed in rats/mice and rats, respectively.

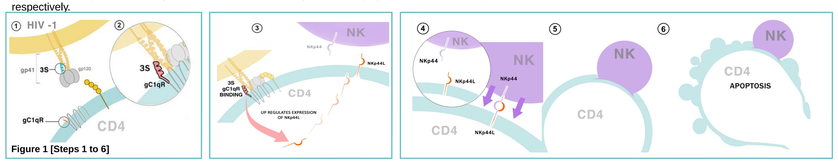


Figure 1 [Steps 1 to 6]

[Steps 1 & 2] The gp41 3S motif of HIV-1 binds to its specific receptor (gC1qR) on CD4.

[Step 3] This interaction induces a molecular pathway that leads to NKp44L expression at the surface of CD4

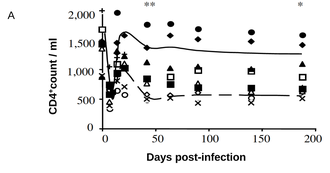
[Steps 4 to 6] NKp44L is the natural ligand of NKp44, which is expressed on activated Natural Killer cells (NK). NKp44L/NKp44 interaction provokes NK-mediated cytotoxicity via apoptosis and CD4 depletion. The apoptosis of CD4 may indirectly induce inflammation and chronic immune activation.

Adapted from Vieillard V et al, PNAS 2005.

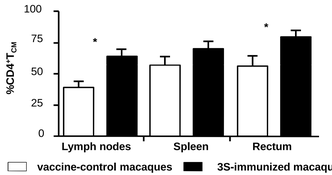
II ● Overview of Experimental Results of Potential VAC-3S Vaccine Properties

Figure 2A, 2B: VAC-3sS Impact on Immunologic Endpoints in a Cynomolgus/SHIV$_{162P3}$ Model

IVAC-3S Immunotherapy Protects CD4 Peripherally and Centrally



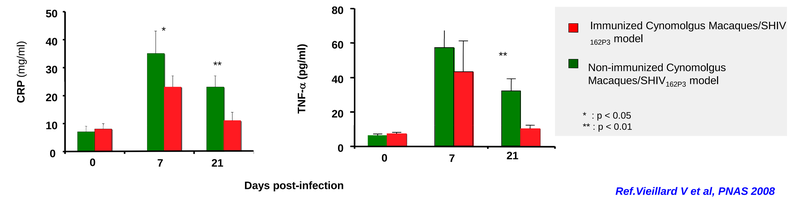
[A] Absolute count of CD4 in peripheral blood from macaques immunized with KLH/3S (closed symbols; black line) and control KLH (open symbols, dotted line).



[B] Absolute CD4+ counts from secondary lymphoid tissues of 3S-vaccinated macaques (closed bars), compared with controls (open bars).

Ref. Vieillard V et al, PNAS 2008; Vieillard V et al, Vaccine 2012

Figure 3A, 3B: VAC-3S Anti-inflammatory Effect in a Cynomolgus/SHIV$_{162P3}$ Model



Ref.Vieillard V et al, PNAS 2008

Table 1: Correlation of anti-3S antibodies and HIV proviral DNA in a Clinical Cohort

In a well-characterized cohort of 244 untreated HIV-1 seroconverters (SEROCO) high levels of anti-3S antibodies (≥50 U/ml) significantly delay spontaneous disease progression in the first years after seroconversion; this effect was not mediated through baseline viral load nor CD4. Additionally, patients with anti-3S Ab ≥ 50 U/ml had lower cellular DNA levels (p<0.0001) in presence of lower serum viral RNA levels (p=0.0004) whilst CD4 counts did not differ between the groups of patients with anti-3S Ab < 50 U/ml or ≥ 50 U/ml;

TABLE 1. Relations Between Anti-3S Ab and the Baseline Characteristics of Patients From the ANRS SEROCO Cohort

	Anti-3S Ab (Ul/mL)		
Characteristics	**<50, n = 114**	**≥50, n= 130**	
Viral DNA, copies/mL, Log_{10}*	**3.0 (2.7 3.3)**	**2.7 (2.3 3.1)**	**<0.0001**

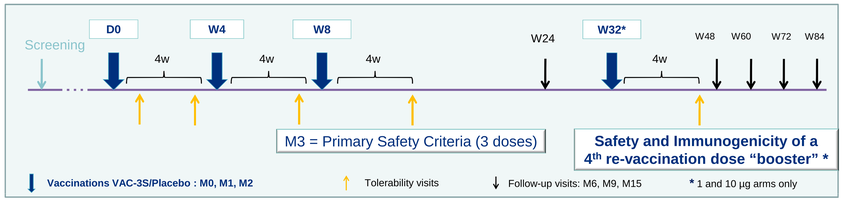
***Data are presented as median (interquartile range).**

Ref. Vieillard V et al, J Acuir Immune Defic Syndr 2012.

Phase I Study: Methods

- Prospective, randomized, placebo-controlled, double-blind dose-escalation study designed to assess safety and immunogenicity of 0.1, 1, 10 µg of 3S antigen present in VAC-3S with 3 IM immunizations at Day0, W4, W8, and a fourth immunization at W32 for the 1 and 10 µg arms [*Figure 2*].
- Primary objective : safety & tolerability
- Secondary objectives : immunogenicity, plasma anti-3S Ab titers, NKp44L expression on CD4+ T cells, CD4+, CD8+ T cell count and percentages, CD4/CD8 ratio, expression of markers of lymphocyte activation (CD25, CD38, HLA-DR) on CD45+CD3+CD4+, CD45+CD3+CD8+ and CD45+CD3-CD8+ cells, expression of markers of lymphocyte differentiation (CCR7, CD45RA) on CD45+CD3+CD4+ and CD45+CD3+CD8+ cells.
- Inclusion and non-inclusion criteria included but were not limited to the following : Patients on antiretroviral therapy (ART) ≥ 1 year, CD4 count at entry ≥ 200 c/mm^3, Nadir CD4 count ≥ 100 c/mm^3, no immunotherapy within the past 12 months, no vaccination within the past quarter.

Figure 4: VAC-3S Immunization Schedule



Twenty five virologically controlled HIV-1 pts (23 men) under ART with CD4 counts >200 c/mm^3 were randomized. Median (Min-Max) age was 47 years (32-54), CD4 710 c/mm^3 (311-1187), CD4 nadir 336 c/mm^3 (127-739), ART initiated median 3.0 yrs (1.1-7.1), none had detectable HIV RNA at inclusion.

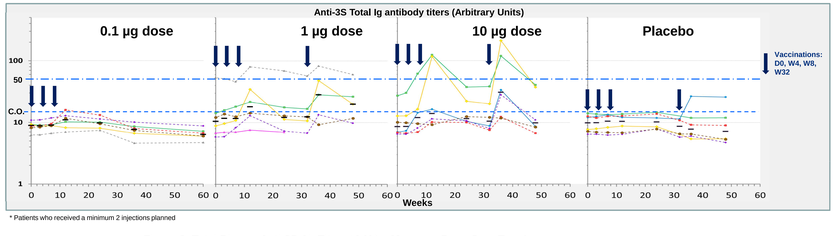
Phase I Study Results: Immunogenicity

Table 2: Demographic Characteristics in VAC-3S Study Groups, Safety Population*

Characteristics mean values ±SD*	Group Dose 1 0.1 µg ● N=6	Group Dose 2 1 µg ● N=6	Group Dose 3 10 µg ● N=6	Placebo Group 0 µg ● N=7
Gender M/F	6/0	5/1	6/0	6/1**
Age, yrs	41 ± 8	48 ± 6	44 ±5	49 ± 6
Weight. kg	74 ± 12	75 ± 13	71 ± 7	77 ± 10
BMI	25 ± 5	24 ± 4	24 ± 1	25 ± 5
Enrolled Completed Vaccination Schedule	6/6	5/6	6/6	6/6
CD4 count nadir at baseline c/mm^3	335 ± 60	331± 145	459 ± 229	292± 94

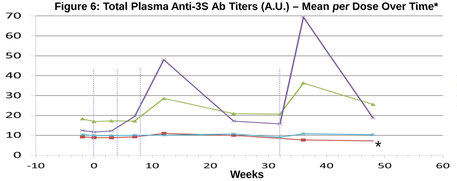
** Patients who received at least one injection, as treated)* ** No decimals included, values rounded up or down *** 1 patient was replaced

Figure 5: Assessment of VAC-3S Dose & Pilot Evaluation of Immunization Schedule. Results shown are in modified as Treated mode*
Base immunization: 3 IM injections q4weeks; Re-immunization "booster" dose: 24 weeks after base immunization (medium and high dose arms only).



* Patients who received a minimum 2 injections planned

Figure 6: Total Plasma Anti-3S Ab Titers (A.U.) – Mean *per* Dose Over Time*



Vaccinations

AU=Arbitrary Units.

* The 0.1 dose µg arm did not receive the 4th Vaccination.

modified As Treated (mAT) Population.

Phase I Study Results: Immunologic Endpoints & Safety

Table 3: Immunological outcome with VAC-3S Vaccination (mAT population)

		Group Dose 1 0.1 µg; N=6		Group Dose 2 1 µg; N=6		Group Dose 3 10 µg; N=6		Group Placebo N=6	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
CD4 counts	Day 0	778	216	592	181	735	101	696	150
	Week 12	676	205	671	142	806	117	745	187
	Week 36	710	129	599	245	723	163	772	297
CD4 %	Day 0	37	5	36	6	35	7	37	4
	Week 12	37	4	33	1	35	9	35	5
	Week 36	38	5	36	4	37	8	35	4
CD8 counts	Day 0	815	282	728	262	896	294	730	275
	Week 12	702	289	983	291	1013	310	830	331
	Week 36	686	144	761	323	793	192	885	469
CD8 %	Day 0	38	6	45	9	42	8	39	7
	Week 12	37	6	48	9	42	9	38	9
	Week 36	37	6	45	11	40	10	38	10
CD4/CD8 ratio	Day 0	1.0	0.2	0.8	0.3	0.9	0.3	1.0	0.3
	Week 12	1.0	0.2	0.7	0.1	0.8	0.4	0.9	0.3
	Week 36	1.0	0.3	0.8	0.3	1.0	0.4	0.9	0.3
% NKp44L on CD4	Day 0	0.5	0.2	0.6	0.1	0.9	0.2	0.8	0.3
	Week 12	1.0	0.3	0.9	0.2	0.8	0.3	0.8	0.2
	Week 36	0.9	0.2	1.1	0.5	0.9	0.2	0.8	0.1
naive CD4	Day 0	39	14	25	9	31	12	37	3
	Week 12	35	9	28	10	31	10	39	6
	Week 36	38	11	27	7	28	12	35	11
Central Memory CD4	Day 0	28	8	30	9	28	5	30	5
	Week 12	26	6	31	9	28	4	28	9
	Week 36	27	7	23	15	22	4	28	8
Activation CD4 (HLA-DR+CD4+)	Day 0	11	6	18	5	17	9	17	5
	Week 12	14	4	21	5	13	6	14	6
	Week 36	11	3	18	7	15	8	15	5
Activation CD8 (HLA-DR+CD38+CD8+)	Day 0	8	7	12	7	12	3	16	14
	Week 12	10	5	20	16	11	4	16	17
	Week 36	6	4	24	24	12	6	17	12

Table 4: VAC-3S Primary Endpoint: Safety & Tolerability (Safety population)

		0.1 µg N=6		1 µg N=6		10 µg N=6		Placebo N=7	
		Event	Subject	Event	Subject	Event	Subject	Event	Subject
Intensity	NSAEs	25	6	57	6	38	6	50	7
	Grade1	20	6	41	6	31	6	34	7
	Grade2	5	3	15	4	7	3	13	6
	Grade3	0	0	1*	1	0	0	1*	1
	Grade4	0	0	0	0	0	0	2°	2
	Leading to corrective treatment	*13*	*5*	*20*	*6*	*7*	*4*	*9*	*6*
	Leading to treatment discontinuation	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*1*
	SAEs	0	0	1*	1	0	0	0	0
Relationship	Related	12	5	28	6	22	6	21	5
	Expected local	7	4	21	5	14	6	12	4
	Erythema	*0*	*0*	*0*	*0*	*1*	*1*	*1*	*1*
	Induration	*1*	*1*	*4*	*1*	*1*	*1*	*3*	*2*
	Pain	*6*	*3*	*17*	*5*	*12*	*6*	*8*	*4*
	Expected systemic	3	3	3	2	4	1	6	4
	Asthenia/Pyrexia	*1*	*1*	*1*	*1*	*2*	*1*	*3*	*3*
	Myalgia	*1*	*1*	*0*	*0*	*1*	*1*	*2*	*1*
	Headache	*1*	*1*	*2*	*2*	*1*	*1*	*1*	*1*
	Other	2	1	4	3	4	4	3	2
	Not related	13	5	30	6	16	4	29	6

* Back Pain Not Related + Myalgia Possibly Related
° Hepatic Cytolysis Unlikely Related / High CPK Not Related

Conclusions

We have developed a novel immunotherapeutic vaccine (VAC-3S) directed to the gp41 3S motif of HIV-1. Anti-3S antibodies can have a key role to shield the immune system and reconstruct physiologic immune homeostasis, complementary to antiretrovirals (ART). VAC-3S is safe at doses studied and immunogenic. Boosting seems of interest. Further dose escalation to 20 µg is completed. Planning for high dose & comprehensive biomarker assessment is also completed, phase II study set up is in progress.

Perspectives

The pathophysiology of HIV disease is dominated by the dynamics between the pathogenic effects of the replicating viral infection and opposing immune system. Firstly, we hypothesize that HIV management, in certain subgroups of patients, can be optimized with a combination of antiretrovirals and an immunotherapeutic vaccine with multiple characteristics including, protection of uninfected CD4 cells, anti-CD4 apoptosis and anti-inflammatory properties. Secondly, a significant amount of research is being carried out to achieve functional cure of HIV. Functional cure has been described as host-mediated control of HIV replication. For this approach, we hypothesize that vaccine-induced anti-3S antibodies can have a key role in a multi-therapeutic approach to cure HIV. 3S antibodies will allow to shield the immune system and reconstruct physiologic immune homeostasis. VAC-3S can potentially complement other therapeutic agents aimed at generating potent responses against the HIV reservoirs.

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