

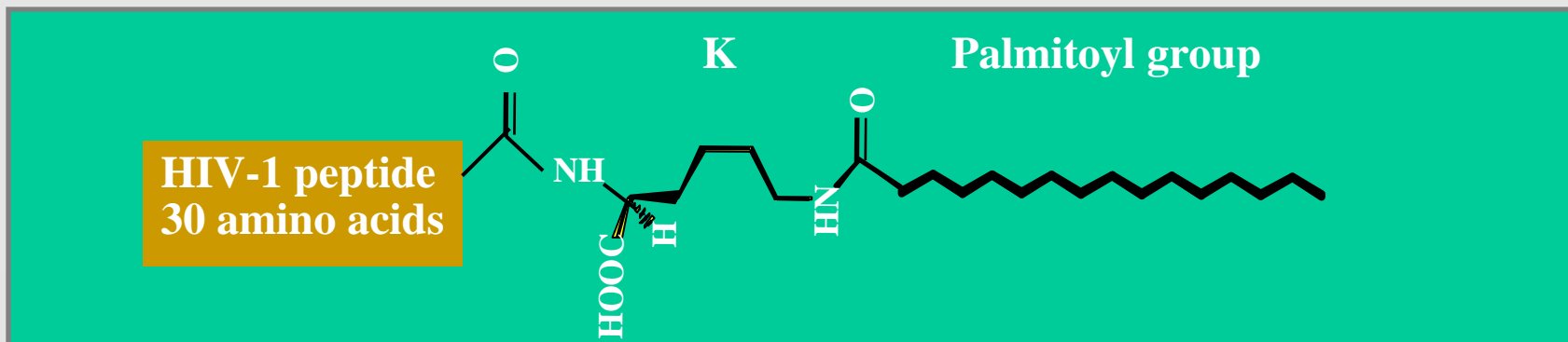
Comparison of safety and Immunogenicity of three doses of HIV-LIPO-5, an HIV-1 lipopeptide vaccine in healthy volunteers - ANRS VAC 18.

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HIV-1 Lipopeptides

- . Synthetic peptides coupled to a palmytoyl lipid tail



- . The lipid tail facilitates entry into the dendritic cells.
- . Combination of various HIV lipopeptides are used together in order to increase polyepitopic responses.
- . HIV-1 lipopeptides have been shown to induce cellular immune responses in mice, primates and humans.
- . Acceptable safety

Mortara, J. Virol. 1998, Vitellio, J. Clin. Invest. 1995, Gahéry-Ségard, AIDS Res Hum Retroviruses 2007, Pialoux, Clin Vaccine Immunol. 2007, Launay PloS One 2007

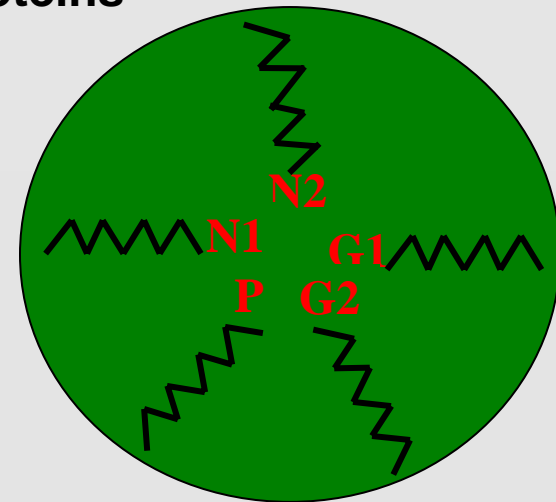
HIV-1 LIPO-5 vaccine

- **LIPO-5**

- mixture of 5 synthetic lipopeptides
- sequences representing CTL epitopes of proteins
 - Gag (aa 17-35 et aa 253-284),
 - Pol (aa 325-355)
 - Nef (aa 66-97 et aa 116-145)
- Produced by Sanofi Pasteur

- **Placebo**

- 5% glucose tris HCl solution
- IM immunization after reconstitution in a 5% glucose tris HCl solution



Slide 3

d1

JG comment formuler le fait qu'on a changé de diluant en cours d'essai ?

ceron, 8/14/2004

Objectives

- **Primary**

- To compare cellular immunogenicity of three different doses of HIV-1 LIPO-5, versus placebo in human healthy volunteers

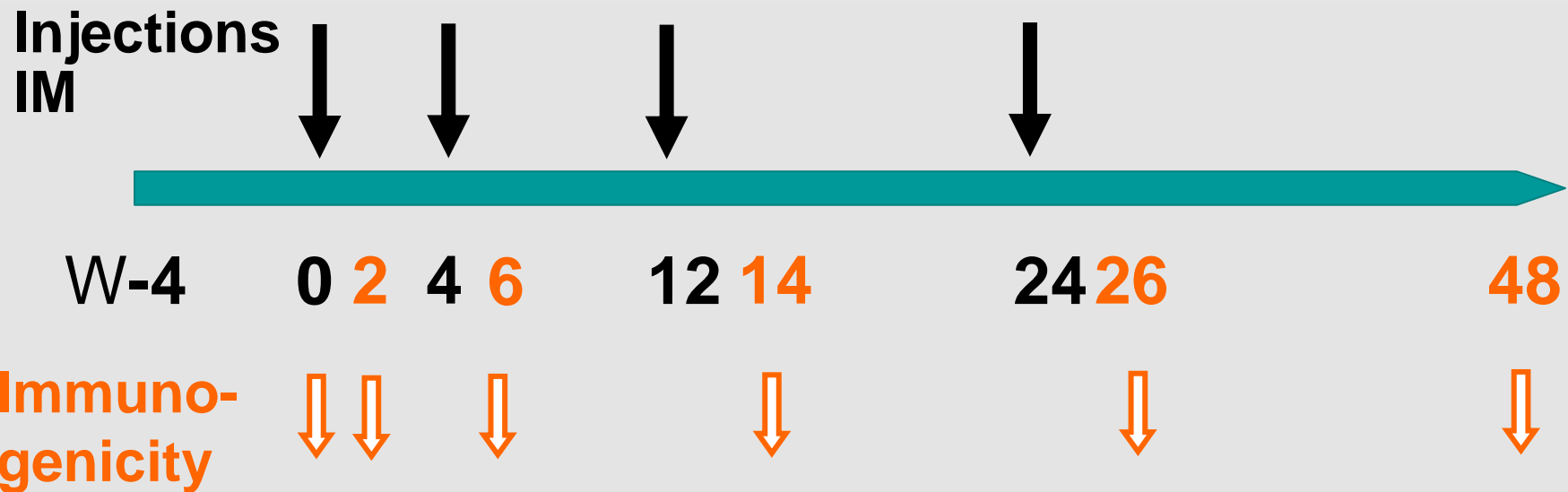
- **Secondary**

- To compare safety of three different doses of HIV-1 LIPO-5 versus placebo

ANRS VAC18 Trial design

Multicenter (6 sites), randomized, double-blind

HIV-uninfected healthy volunteers, 21-55 years,
at low risk of HIV infection, pre-screened by the ANRS



ANRS VAC18

Arm	Doses IM	Subjects	W0	W4	W12	W24
A	500 µg	33	LIPO-5	LIPO-5	LIPO-5	LIPO-5
B	150 µg	33	LIPO-5	LIPO-5	LIPO-5	LIPO-5
C	50 µg	33	LIPO-5	LIPO-5	LIPO-5	LIPO-5
D	Placebo	33	X	X	X	X

Primary end point:

- CD8 T-cell responses (IFN- γ ELISpot on PBMC cultured 12-days)

Secondary end points:

- Safety : grade \geq 2 local and systemic reactions
- *Ex vivo* CD8 T-cell responses (IFN- γ ELISpot)
- Polyepitopic / durable CD8-T cell responses
- CD4 T-cell responses (PBMC lymphoproliferation)

Criteria for positive CD8+ and CD4+ responses

CD8+ responses:

- > 100 SFU/ 10^6 PBMC for mean of 3 wells
- and ≥ 3 -fold higher than unstimulated wells
- and found at least twice throughout the follow-up (W2 to W26) for a given pool

CD4+ responses:

- Stimulation index (cpm of quadruplicate wells/median background cpm) ≥ 3
- and net cpm > 3000

Sample size

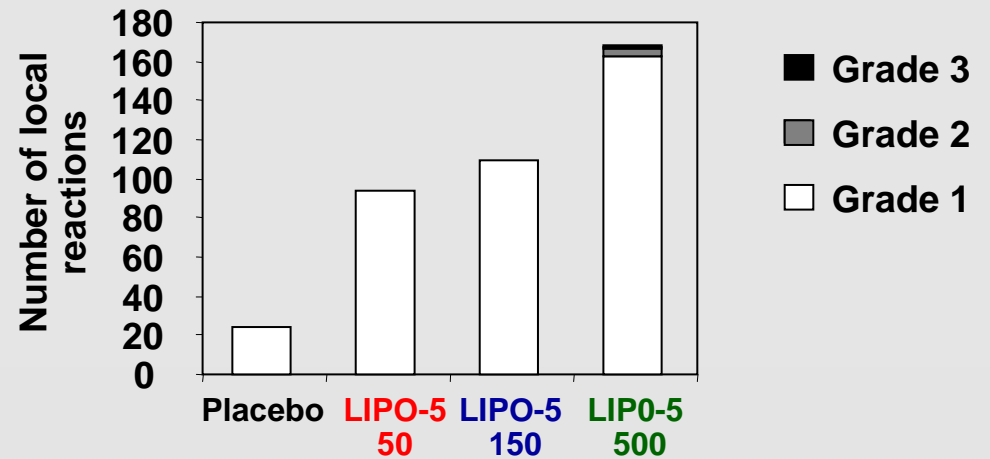
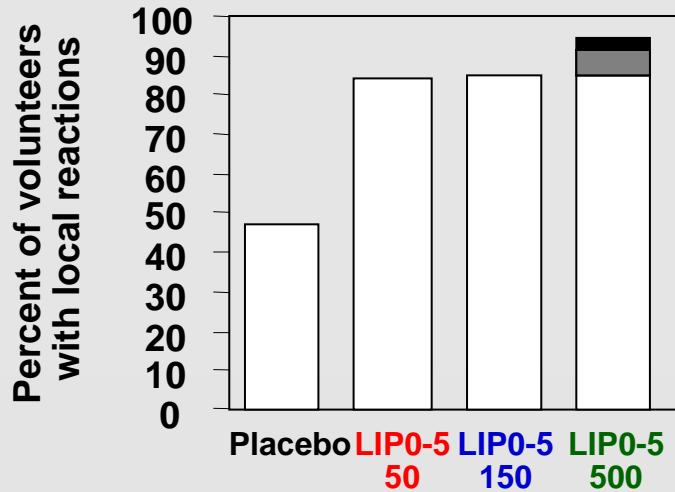
- **Superiority** of HIV-LIPO-5 over placebo in eliciting CD8+ T cell sustained response (primary endpoint).
- **Sample size** : 30 subjects per arm with 80% overall power and 0.05 overall type I error, allowing pairwise comparisons of LIPO-5 arms vs. placebo (Bonferroni-Holm correction).
- **Hypothesis** : 10% placebo / 50% LIPO-5
- **Randomization** with 1:1:1:1 ratio (10% non assessable)

Participants and follow-up

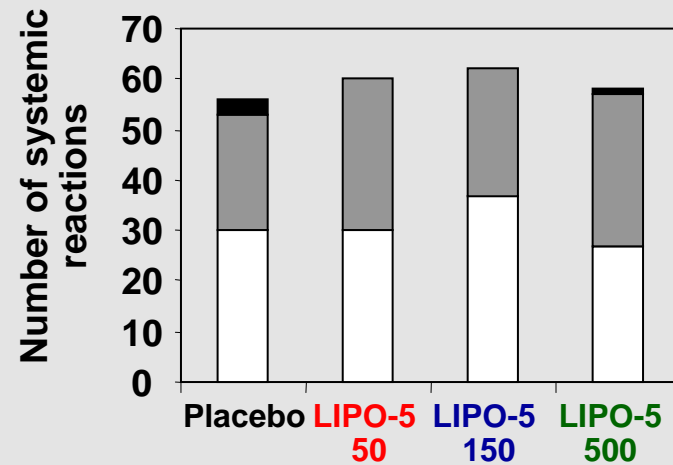
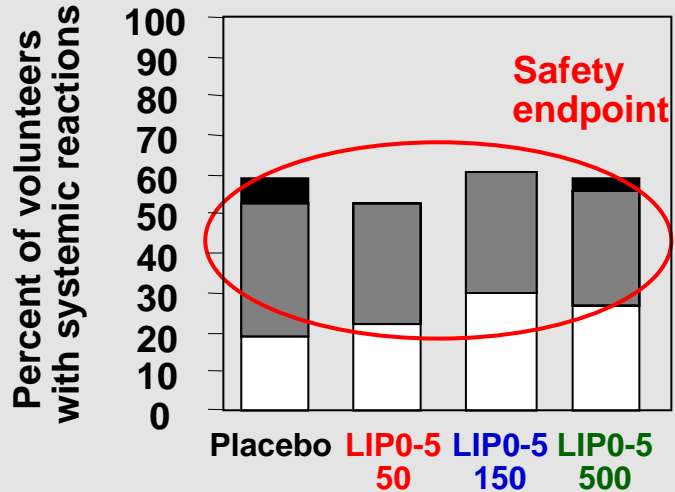
- **132 volunteers were enrolled and randomized**
- **131 were analyzed (1 did not receive any injection)**
 - **Male : 56.5 %**
 - **Median age : 43.5 (23-55)**
- **87.5% received all 4 injections**
- **2 participants were lost to follow-up at week 48**

Local and systemic reactions

LOCAL



SYSTEMIC



Local and systemic reactions (2)

Severe adverse events (n=7)

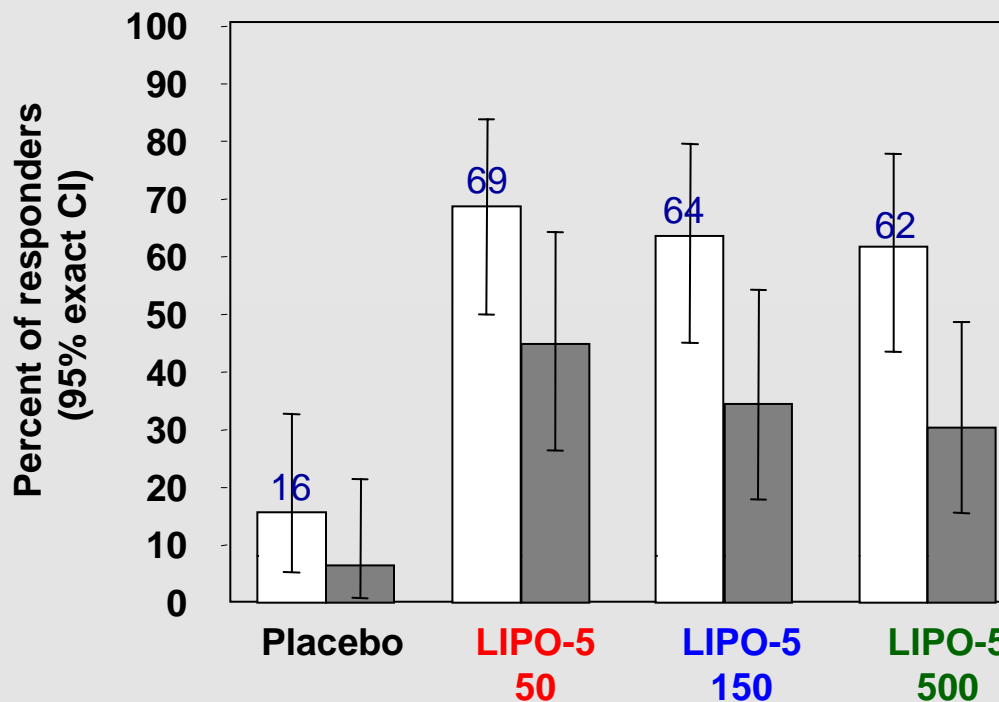
- 4 in placebo group: hypereosinophilia, paresthesia, rhabdomyolysis, proteinuria
- 3 in LIPO-5 groups: CPK elevation, malaise, uterus fibroma

Biological events

- No significant trends or abnormalities
- Positive auto antibodies : 5/32 (15.6%) in placebo group vs 8/99 (8.1%) in LIPO-5 groups (p=0.30)

CD8+ responses by ELISpot Interferon- γ

Percentage of responders



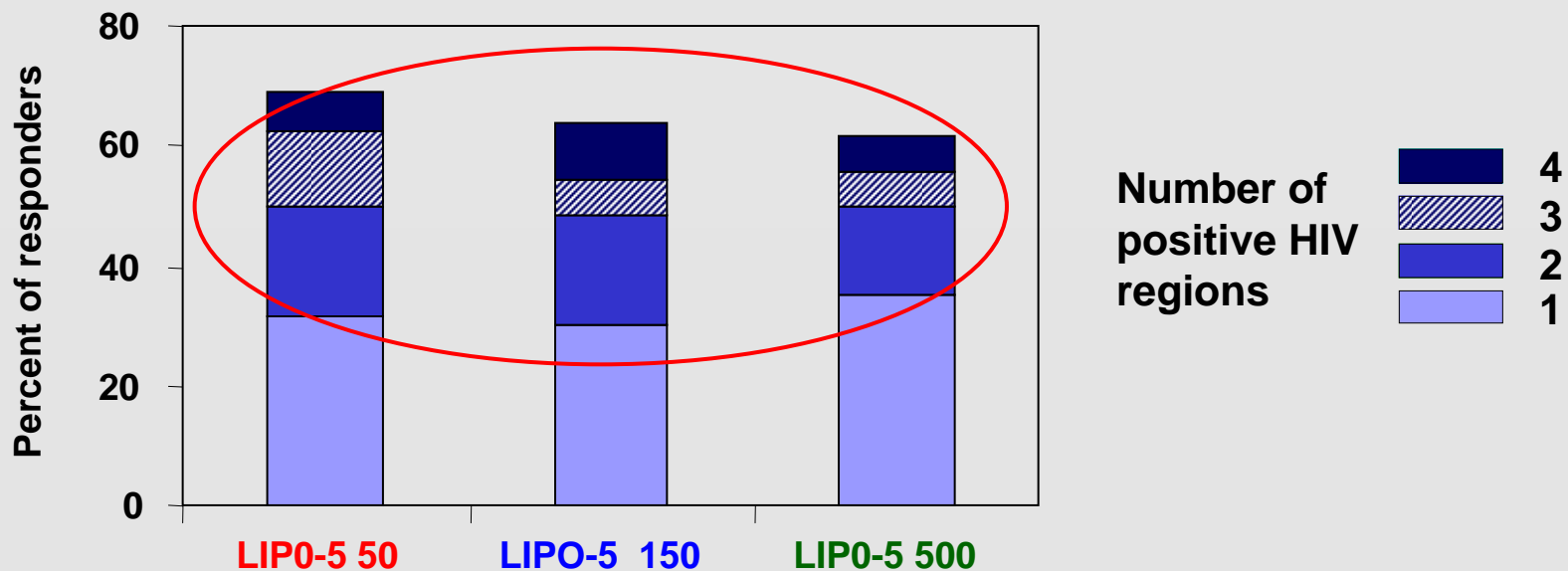
$P \leq 0.0001$ for all comparisons to Placebo

- Sustained response from w2 to w26 *
- Sustained and durable response at w48

* % volunteers with sustained response to the same HIV peptide pool at least on 2 occasions from week 2 to week 26

CD8+ responses by ELISpot Interferon- γ

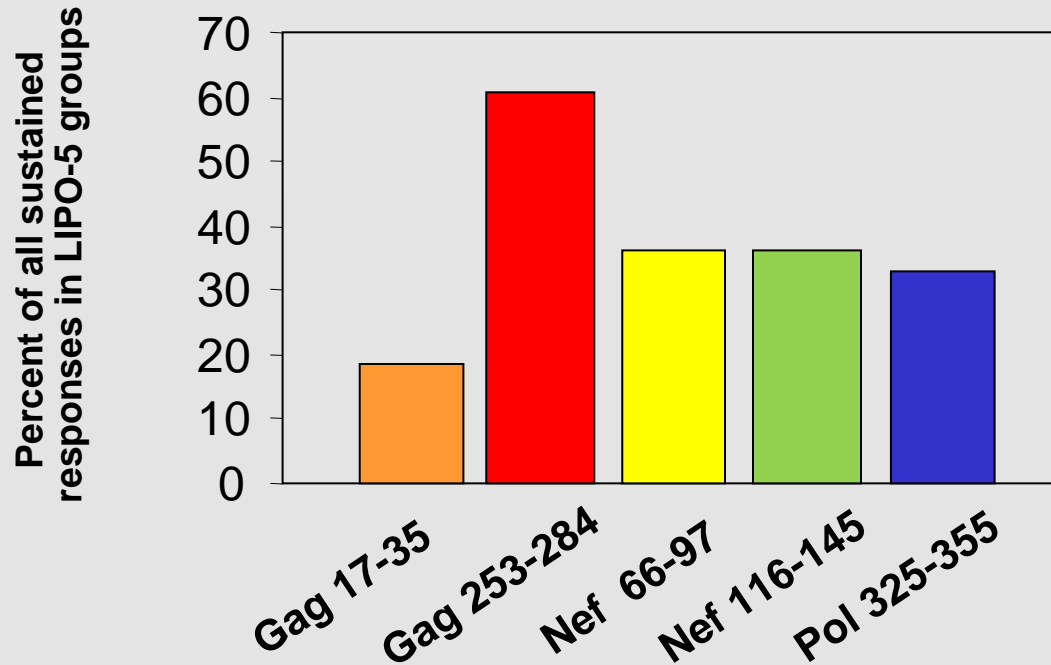
Polyepitopic responses: % of responders



Responses to more than 1 HIV-region : LIPO-5 groups 32.3% vs Placebo group 0%
 P<0.0001

CD8+ responses by ELISpot Interferon- γ

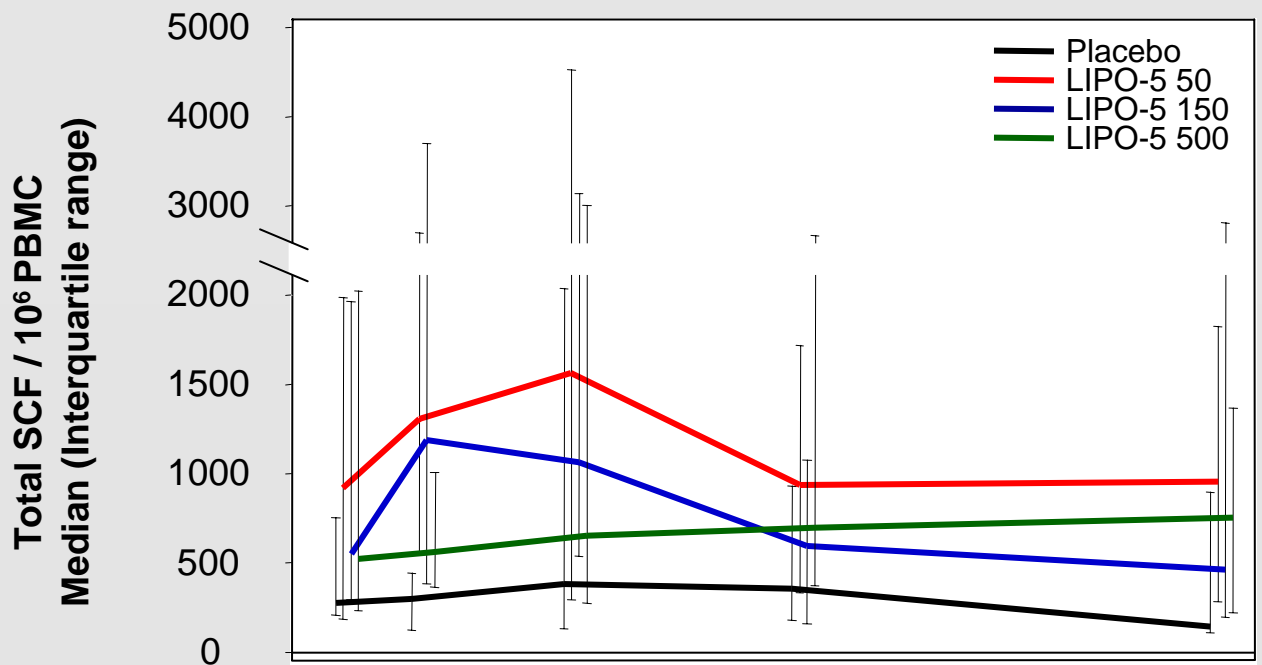
HIV regions recognized : % of sustained responses



64 responders in LIPO-5 groups

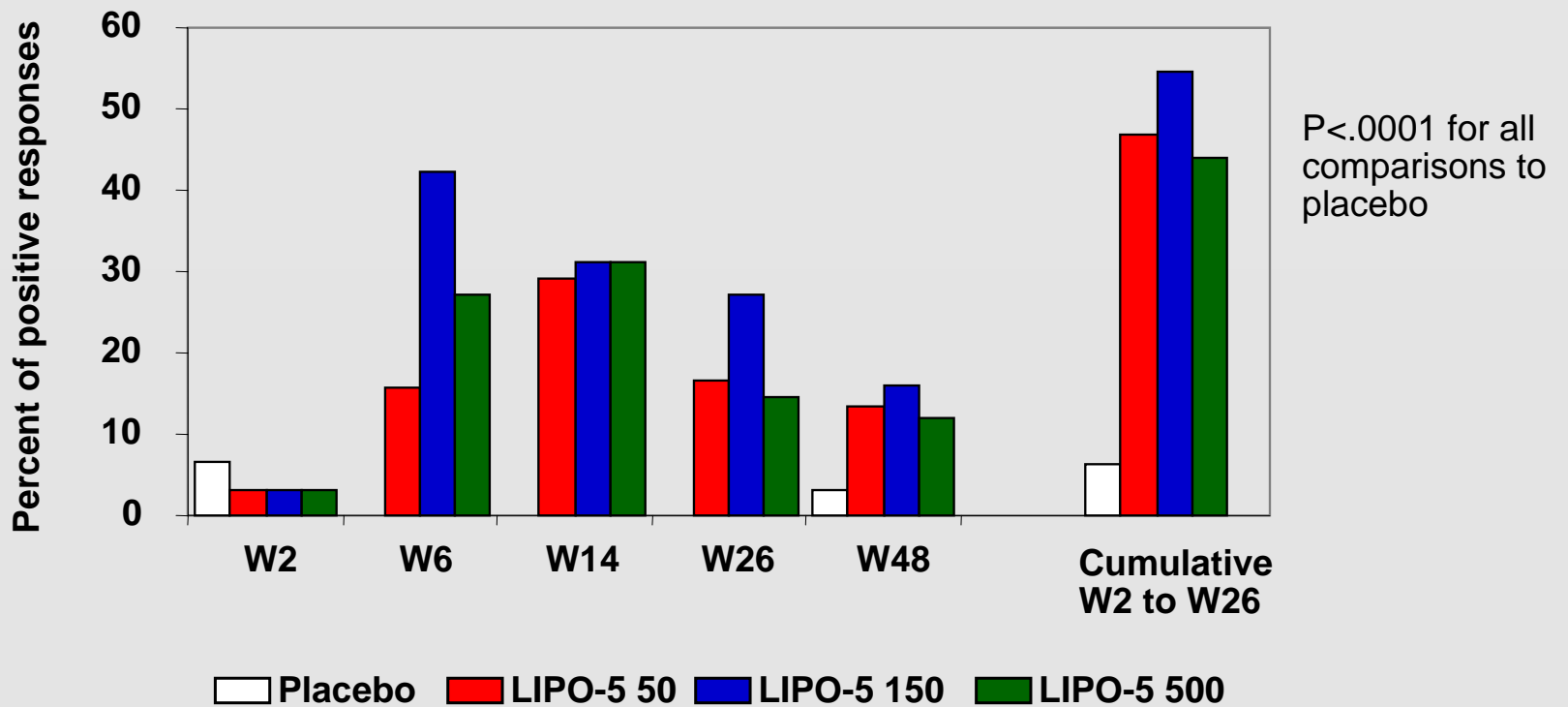
CD8+ responses by ELISpot Interferon- γ

Kinetic and magnitude of response



	W2	W6	W14	W26	W48
Placebo	4	10	8	10	4
LIPO5-50	16	21	21	22	16
LIPO-5 150	11	20	21	19	14
LIPO-5 500	17	21	20	23	17

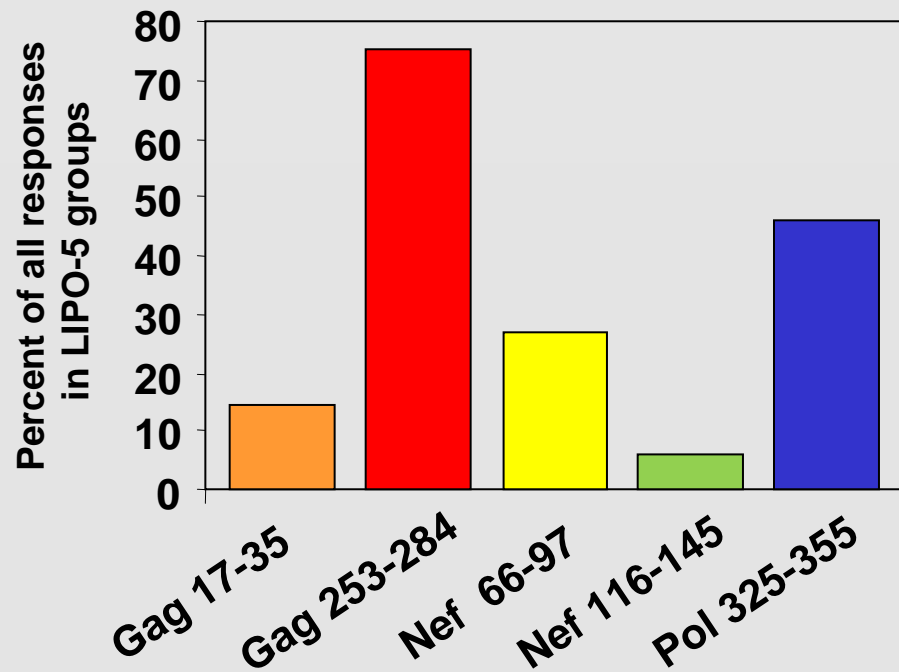
CD4+ responses by lymphoproliferation



Positive responses to at least one HIV-1 peptide (SI \geq 3 and net cpm > 3000).
 Two responses detected at week 0 (in Placebo and LIPO-5 500 groups) were not positive after immunization.

CD4+ responses by lymphoproliferation

HIV region recognized: % of all responses (W2 to W26)



48 responders in LIPO-5 groups (cumulative W2 to W26)

Conclusions

- In this placebo-controlled trial, HIV LIPO-5 vaccine was shown to induce :
 - CD8+ T cell responses in 65-69 % of healthy volunteers, that were polyepitopic in 32%
 - CD4+ T cell responses in 50%
 - with similar rates of responses in the three doses groups
- The three doses were well tolerated. However fewer local reactions were observed for the lowest dose
- The lowest dose of 50 μ g appears to be appropriate to be used in further « prime-boost » trials>

VAC18 ANRS STUDY GROUP- Acknowledgements

- **Participating sites :**

CIC Vaccinologie Cochin-Pasteur, Paris: O Launay, C Desaint, B Silbermann, L Belarbi, P Duchet-Niedziolka, B Phung, Z Absi

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Hôpital Henri Mondor, Créteil: JD Lelièvre, M Berdah

Hôpital Purpan, Toulouse: L Cuzin, M Obadia

Hôpital Sainte-Marguerite, Marseille: I Poizot-Martin, MP Drogoul-Vey

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- B Weill for reviewing auto-antibody events.
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- **Sanofi Pasteur**
- The authors fully acknowledge the participation of all the **study volunteers**