# UN-ADJUVANTED CD40.HIVRI.ENV VACCINE LATE BOOST INDUCES DURABLE IMMUNE RESPONSES: ANRS VRI06 TRIAL

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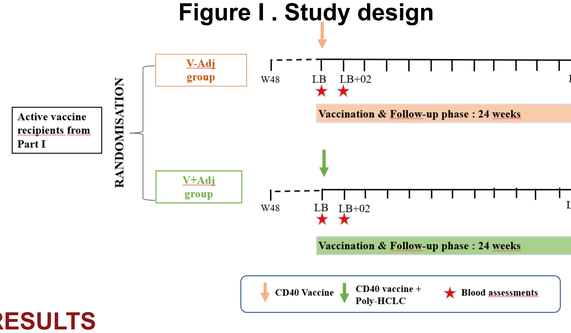
## BACKGROUND

CD40.HIVRI.Env is a gp140 Env (Clade C 96ZM65) fused to an anti-CD40 mAb to target CD40-expressing dendritic cells. The ANRS VRI06 phase I trial (NCT04842682) enrolled 72 non HIV-infected volunteers to receive either 0.3, 1.0, or 3.0 mg of CD40.HIVRI.Env (Hiltonol® adjuvanted) alone or co-administered with DNA-HIV-PT123 at weeks (W) 0, 4 and 24, randomized 5:1 active vs. placebo. Results showed good safety and strong immunogenicity of vaccines until W48 regardless dose or combination *(Lévy et al. EClinicalMedicine 2024)*.

## METHODS

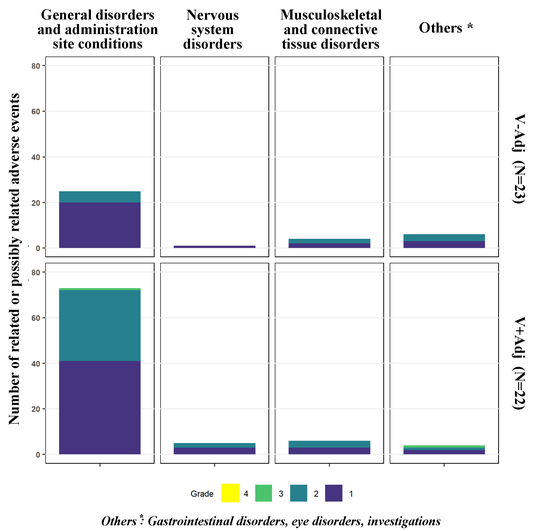
Beyond W48 of the trial, active vaccine recipients were again randomized to receive one late boost (LB) of CD40.HIVRI.Env (0.3mg) either with Hiltonol® (V+Adj) or not (V-Adj). Safety and immunogenicity (anti-Env and anti V1/V2 IgG, neutralizing antibodies, T-cell responses) were evaluated at 2 and 24W after LB (LB+02, LB+24).

**Figure I . Study design**




## RESULTS

**Figure II. Solicited adverse events**




*Others* : Gastrointestinal disorders, eye disorders, investigations*

**A single additional late injection of CD40.HIVRI.Env**, even unadjuvanted, **boosted immune responses**, including **anti-V1V2 and neutralizing antibodies.**

Forty-five volunteers (mean age 35 years, 56% male) were randomized. Demographics and immune responses were similar between groups at LB visit. LB interval (median; IQR) since VRI06 baseline was 80W [75;104] in V+Adj (n=22) and 79W [65;101] in V-Adj (n=23).

### Safety

LB vaccination was safe and well tolerated. Most of the vaccine related AE were associated with systemic and local reactogenicity. They were mainly mild to moderate in severity and resolved within around three days.

### Immunogenicity

IgG response rates* against vaccine-matched (gp140 ZM96) and 9 heterologous gp120/gp140 antigens were 50-100% at LB,100% and 82-100% at LB+02 and LB+24, respectively. Increases > 1 log10 in the magnitude of IgG responses (MFI) to antigens were observed at LB+02 relative to LB. Response rates to gp70 V1V2 antigens raised from 0-4% at LB to 45-55% (autologous 96ZM651), 26-27% (92TH02), 61-68% (CE1086), 61-77% (CaseA2) across groups at LB+02.

**Figure III. IgG anti-Env response**

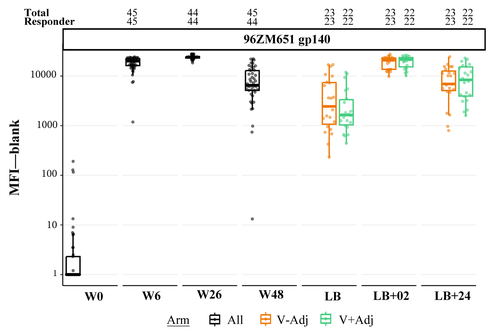
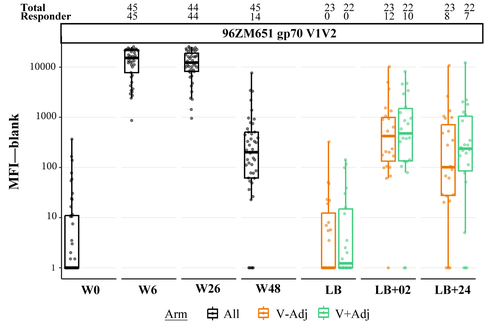
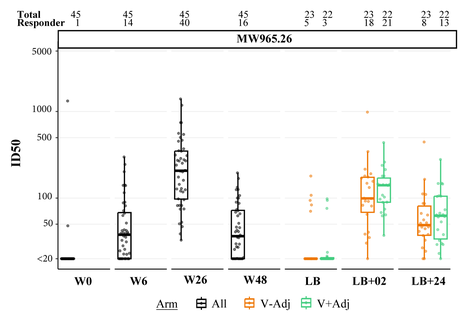



**Figure IV. IgG anti-V1V2 response**




Neutralizing antibody IC50 titers against Tier1 MW965.26 were detected in 14-22% at LB and 78-95% and 35-59% at LB+02 and +24.

**Figure V. Neutralization against MW965.26**




*IgG response rate definition for each group, isotype and antigen :
- Post vaccination MFI-blank ≥ the 95th percentile of MFI-blank distribution at W0, and
- MFI-blank > 3 × MFI-blank at W0

**Figure VI. Env-specific CD4+ T cells response**

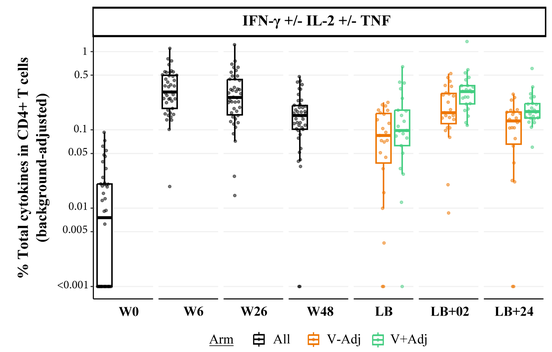



**Figure VII. Polyfunctionality of Env-specific CD4+ T cells**




Frequencies (median [IQR]) of polyfunctional Env-specific CD4 T cells (IL-2+/-IFN-γ+/-TNF) were 0.09 [0.05;0.18] at LB and raised to 0.26 [0.15;0.36] and 0.15 [0.11;0.20] at LB+02 and +24, respectively. No consistent substantial differences were noted between Adj+ and Adj- recipients.

## CONCLUSIONS

Follow-up after initial CD40.HIVRI.Env vaccination showed the persistence of anti-Env antibodies and CD4 responses more than one year after the last injection (W26 of the VRI06 trial). A single additional late injection of CD40.HIVRI.Env, even unadjuvanted, boosted immune responses, including anti-V1V2 and neutralizing antibodies.

**Acknowledgements**:
We are grateful to all trial volunteers and to all members of the ANRS VRI06 protocol team and committees.
**Trial steering committee**: Candotti F. Centlivre M., Desvallées M., Durand M., Diallo A., Ding S., Hanot L., Hardel L., Hocini H., Lacabaratz C., Lelièvre J.-D., Levoyer L., Lévy Y., Mercier N., Moog C., Pantaleo G., Paul S., Richert L., Rieux V., Thiébaut R., Surgers L., Wiedemann A.. **Data and safety monitoring board**: Batteux F., Grabar S., Pollard H., Viard J.-P.. **Clinical Trial Unit UMS 54 MART, Inserm/Univ Bordeaux:** Desvallées M., Durand M., Hardel L., Pinoges L., Richert L., Wittkop L.. **Clinical centers (investigators):** Créteil (Lelièvre J.-D.), Paris-Cochin (Launay O.), Lausanne (Candotti F.).
This clinical trial ANRS VRI06 was sponsored by Inserm-ANRS and funded by the VRI (ANR-10-LABX-77) and the ANRS Emerging infectious diseases (ANRS MIE). Trial conducted with the support of Oncovir. Inserm Transfert provided a license for CD40 targeting vaccines to the biotech company LinKinVax/EnnoDC.