



# Long term vaccine-induced HIV seropositivity among HIV uninfected healthy volunteers in ANRS COV1-COHVAC cohort

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## ABSTRACT

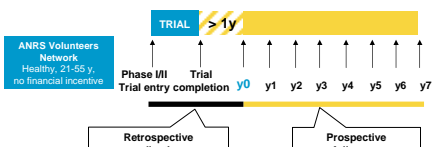
**Background:** Long term vaccine-induced HIV seropositivity (VISP) remains to be studied in HIV uninfected vaccine healthy volunteers who participated in early phase and II trials. ANRS COV1-COHVAC cohort offers the opportunity to evaluate the long term persistence of VISP among such participants.  
**Methods:** In this cross-sectional study, HIV serology was assessed at enrollment in ANRS COV1-COHVAC cohort in volunteers who had received recombinant envelope protein (rgp160), from 1992 to 1993, canarypox vectors (vCP) expressing Env, Gag, Pro and CTL domains of Pol, from 1994 to 2001, and/or HIV-1 lipopeptides representing CTL epitopes of Gag, Pol and Nef proteins, from 1997 to 2007. The vaccines were injected intramuscularly (IM) or intradermally except in one mucosal gp160 trial. VISP was defined as HIV positivity in at least one of two different licensed enzyme immunoassays tests, regardless of Western-blot results.  
**Results:** From December 2008 to September 2010, among 422 volunteers who had received a candidate vaccine, 257 (61%) were enrolled in COHVAC and 239 samples were tested. The median duration since the first injection was 5.2 years (range, 2.2 to 17.6). The median age was 52 years (range, 25 to 71) and 53% were male. VISP was observed in 25 volunteers (10.2%, 95% confidence interval [CI]: 6.9%-15.1%); 17 of 26 (65.4%, 95%CI: 34.3%-82.8%) IM rgp160 recipients, 7 of 42 (16.7%, 95%CI: 7.0%-26.4%) recipients of vCP products without rgp160 and 1 of 150 (0.6%, 95% CI: 0.0%-3.7%) lipopeptide-alone products recipients. None of the 21 (0%, 95%CI: 0.0%-16.1%) mucosal gp160 recipients had VISP. Western-blot showed presence of bands included in the vaccine products (mainly gp160, p24, p25) in 1% of subjects tested. For rgp160 and vCP recipients with VISP, the median duration since the first injection was 16.5 years (range, 16 to 18) and 6.7 years (range, 3.5 to 12) respectively. None of the volunteers acquired HIV infection.  
**Conclusion:** Long term HIV vaccine-induced antibody detection depends on vaccine construct. A majority of recombinant envelope protein recipients remained HIV seropositive more than 16 years after vaccination. In contrast, vaccine-induced seropositivity was observed only in a minority of Alvac canarypox products recipients 8 years after vaccination and beyond. Long term persistence of vaccine-induced seropositivity should be considered as a possible consequence of HIV preventive vaccine trials and participants informed accordingly.

## BACKGROUND

Long term vaccine-induced HIV seropositivity (VISP) remains to be studied in HIV uninfected vaccine healthy volunteers who participated in early phase I and II HIV preventive vaccine trials.

## METHODS

ANRS COV1-COHVAC : Prospective multicenter cohort study for long term follow-up of safety, serological evolution and evaluation of the consequences of participation in HIV preventive vaccine trials



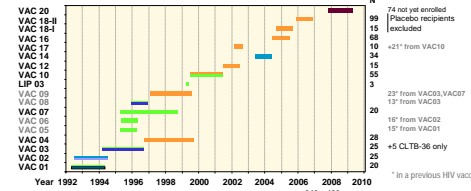
- Primary endpoint** Severe medical events (grade 3-4), neurological, ophthalmological, and immunological events
- Secondary endpoints**
  - Psychosocial and behavioral consequences of participation in HIV vaccine trials
  - Long-term HIV antibody response
  - Incidence of HIV infections

### Cross-sectional study: anti-HIV antibodies at y0 in 2009-2010

- Anti-HIV antibodies tested using 2 different licensed enzyme immunoassays (EIA)** at inclusion in COHVAC (y0)
- Vaccine-induced seropositivity (VISP)** defined as at least one of the two EIA tests positive, regardless of Western-Blot results
- Population** composed of volunteers who have participated at least one vaccine candidate injection and gave consent to participate in prospective follow-up. Recipients were informed about the risk of developing VISP and potential negative consequences thereof before entering in Phase III trials.
- Four categories of volunteers according to HIV vaccine candidate received**
  - rgp160:** recombinant envelope protein subunit gp160, received with or without any other product or adjuvant
  - vCP:** canarypox vectors without rgp160, alone or with HIV lipopeptides
  - LIPO:** HIV lipopeptides alone
  - mucgp160:** mucosal recombinant envelope protein subunit gp160 alone
- Time of injections defined as the first vaccine injection regardless of other injections received by the volunteer.

## RESULTS

### ANRS Phase I/II Trials (422 participants)



**Vaccine candidates**

- ALVAC-HIV canarypox vectors expressing Env, Gag, Pro and CTL domains of Pol (vCP)
- Recombinant envelope protein subunit (rgp160)
- Env V3 MN synthetic peptide (peptideV3)
- P24 / Env V3 MN synthetic peptide (CLTB-36)
- HIV-1 Lipopeptides representing CTL epitopes of Gag, Pol and Nef proteins

All vaccines were injected intra-muscularly, except in VAC14 (mucosal, nasal/vaginal) and in VAC16 (intradermal vs intra-muscular route)

ANRS Centers: n°049: Hôpital Tenon, Paris – n°182: Hôpital Cochin, Paris  
n°059: Hôpital Mondor, Créteil – n°072: Hôpital Ste Marguerite, Marseille  
n°076: Hôpital Hôtel Dieu, Nantes – n°085: Hôpital Purpan, Toulouse

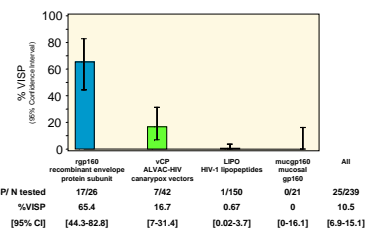
	rgp160	vCP	LIPO	LIPO	mucgp160	All
Trials	VAC01 VAC02	VAC03 VAC07 LIP03 VAC10 VAC12	VAC04 VAC10	VAC16 VAC18	VAC14	
ANRS Centers	049 182	182 059/072 076/085	049/182	049	049	182
Number of participants in trials	45	80	81	182	34	422

### COHVAC population characteristics

	rgp160	vCP	LIPO	mucgp160	All
N in trials	45	80	263	34	422
N enrolled in COHVAC (%)	29 (64)	47 (59)	156 (59)	25 (74)	257 (61)
N tested (%)	26 (58)	42 (53)	150 (57)	21 (62)	239 (57)
Age	Median: 56.6 Min: 43.7 Max: 71.2	Median: 59.1 Min: 39.9 Max: 70.1	Median: 50.8 Min: 25.3 Max: 64.3	Median: 51.5 Min: 36.8 Max: 59.3	Median: 52.5 Min: 25.3 Max: 71.2
Gender	Female: 9 Male: 17	Female: 19 Male: 23	Female: 64 Male: 86	Female: 21 Male: 126	Female: 21 Male: 126
% male	65	55	57	0	53
Time (y)	Median: 16.6 Min: 16.3 Max: 17.5	Median: 14.2 Min: 8.1 Max: 15.6	Median: 4.3 Min: 2.2 Max: 13.2	Median: 5.3 Min: 5.1 Max: 6.5	Median: 5.2 Min: 2.2 Max: 17.5
injections	Dec08 to Mar10	Dec08 to Sep10	Dec08 to Sep10	Dec08 to Mar10	Dec08 to Sep10

N: Number of participants  
\* 18 volunteers not tested; deceased (3); did not accept prospective follow-up and testing (7); tests not done (5); results not available (2); tested but received CLTB-36 only (1)

### Vaccine-induced seropositivity rate (VISP) by vaccine type



### Volunteers presenting vaccine-induced seropositivity (N=25)

Vaccine	Gender	Age	Vaccine Trial	Vaccines received + adjuvant	Time since injections (years)	EIA tests			Western-blot assays
						Genescreen ultra-HIV (BIORAD)	Vidas HIV duo (BIO-MERIEUX)	Anti-HIV TETRA ELISA (BIOTEST)	
rgp160	M	56.6	VAC01	vCP125, rgp160-HFA	16.4	+	+	+	gp160, gp120, p55, p24 (traces)
rgp160	F	68.8	VAC01	vCP125, rgp160-HFA	16.4	+	+	+	gp160 (traces)
rgp160	F	70.3	VAC01	vCP125, rgp160-HFA	16.4	+	+	+	p55, p25
rgp160	M	56.8	VAC01	vCP125, rgp160-HFA	16.4	+	+	+	0
rgp160	F	46.9	VAC01	vCP125, rgp160-HFA	16.3	+	+	+	0
rgp160	M	43.7	VAC02	rgp160-HFA, pep1v3	16.5	+	+	+	0
rgp160	F	64.9	VAC02	rgp160-HFA, pep1v3	16.7	+	+	+	+ / -
rgp160	F	58	VAC02	rgp160-HFA, pep1v3	16.6	+	+	+	0
rgp160	M	54.1	VAC01	vCP125, rgp160-alum	16.4	+	+	+	0
rgp160	M	69.1	VAC01	vCP125, rgp160-alum	16.4	+	+	+	0
rgp160	M	56.3	VAC02	rgp160-alum	16.7	+	+	+	0
rgp160	M	57.5	VAC02	rgp160-alum	16.4	+	+	+	0
rgp160	F	71.2	VAC02	rgp160-alum	16.8	+	+	+	0
rgp160	M	50.1	VAC02	rgp160-alum, pep1v3	16.5	+	+	+	0
rgp160	M	68	VAC02	rgp160-alum, pep1v3	16.7	+	+	+	0
rgp160	F	46	VAC02	rgp160-alum, pep1v3	16.7	+	+	+	0
rgp160	M	48.4	VAC02	rgp160-alum, pep1v3	16.7	+	+	+	0
vCP	F	61.3	VAC03	vCP265, CLTB-36	15	+	+	+	p55
vCP	M	62.9	VAC10	vCP1452	9.7	+	+	+	p55, p25
vCP	F	62.1	VAC10	vCP1452	8.9	+	+	+	p55, p25
vCP	M	48.7	VAC10	vCP1452	8.5	+	+	+	p55, p25
vCP	F	49.9	VAC10	vCP1452	9.8	+	+	+	p55, p25
vCP	M	43.8	VAC10	vCP1452	9.8	+	+	+	p55, p25
vCP	F	60.1	VAC10	LIPO-EIT	8.5	+	+	+	p55, p25, p58
LIPO	M	61.5	VAC10	LIPO-S	9.1	+	+	+	ND (p24 antigen neg)

\* Adjuvants : alum = aluminum hydroxide; HFA = incomplete Freund's adjuvant  
+ Western-blot assays: New LAV Size (BIORAD) / SANOFI DIAGNOSTICS PASTEUR (except one test with Inno-LiA HIVIII (INGENETICS))

None of the volunteers acquired HIV infection.

## CONCLUSIONS

- > Long term HIV vaccine-induced antibody detection depends on vaccine construct.
- > More than 60 percent of recombinant envelope protein recipients remained HIV seropositive more than 16 years after vaccination.
- > In contrast, vaccine-induced seropositivity was observed only in less than 20 percent of Alvac canarypox products recipients 8 years after vaccination and beyond.
- > Long term persistence of vaccine-induced seropositivity should be considered as a possible consequence of HIV preventive vaccine trials and participants informed accordingly.

### ANRS COV1-COHVAC

**Participating Clinical Directors:**  

- AP-HIP Hôpital Cochin, CIC Vaccinologie Cochin-Pasteur, Paris (Dr. Launay)
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- CHU Hôtel Dieu, Nantes (B. Bonnet, P. Morineau, La Houssine, N. Fouillat)
- ANRS Vaccine Research: Y. Lévy, A.L. Ross, V. Rieux, A. Boukane
- Hôpital Purpan, Toulouse (L. Cuzin, M. Chauveau)
- Coordinating Trial Center: INSERM, SC10, Villejuif (J.P. Aboulker, C. Desaint, C. Durier, M. Reich, M. La Couron, S. Droumassy, Y. Saïd, B. Abbadier, C. Moreau)

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