

Research Article

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Long-Term Persistence of Vaccine-Induced HIV Seropositivity in Healthy Volunteers

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Abstract

Objectives: To assess the long-term serological impact of HIV preventive vaccine trial participation, vaccine-induced HIV seropositivity (VISP) was evaluated and related factors were investigated. The anti-HIV antibody reactivity ratio distribution was estimated.

Methods: ANRS COHVAC is an open national prospective multicentre cohort study including healthy volunteers who received at least one dose of vaccine candidate of ANRS HIV preventive vaccine trials since 1992. VISP was studied in a cross-sectional study at the time of the cohort's initial visit, starting in 2008. Anti-HIV antibody detection was performed using the ABBOTT ARCHITECT® HIV Ag/Ac Combo Enzyme Immunoassay (EIA) in a centralized laboratory. A ratio greater than or equal to 1 was considered to define HIV seropositivity.

Results: 293 participants were evaluated for a median period of 6 years (range: 2-18 years) after their inclusion in vaccine preventive trials. The frequency of VISP was estimated at 7.2% (21 out of 293) for all volunteers, and 69.0% (20 out of 29) for volunteers who received recombinant HIV-1 envelope protein, after a median period of 16.6 years after immunization (range: 16.3-18.4). The ARCHITECT test ratio among positive volunteers was low, with a median of 3.02 (range: 1.02 -14.04).

Conclusion: Healthy volunteers should be informed of possible VISP persistence for nearly 17 years, following HIV envelope vaccination inducing antibody responses. A single, routine serology test is unable to differentiate between VISP and a recent HIV infection. The combination of different technologies, applicable to resource-limited settings, is needed to distinguish vaccine-induced seropositivity from an HIV infection.

Keywords: HIV vaccine; Vaccine-induced seropositivity; Immunoassay

Introduction

In the framework of HIV vaccine research programs, phase 2b or 3 preventive trials have already included several thousand healthy volunteers [1-5]. Some of these have developed antibodies to HIV antigens, leading to seropositivity in HIV tests, also defined as vaccine-induced seropositivity (VISP) [6-8]. Addressing VISP is important, as it complicates the detection of "true" HIV infection and may have social implications for volunteers. These consequences may also influence the volunteers' decision to participate in such trials.

Since 1992, approximately 500 healthy French volunteers participated in phase 1 or 2 HIV preventive vaccine trials, under the guidance of the French National Agency for AIDS Research and viral hepatitis (ANRS) [9,10]. The frequency of VISP was previously reported among volunteers of the ANRS network [11], showing that a majority of rgp160 vaccine candidate recipients remained seropositive after 8 years of follow-up. The aim of the present study was to describe, at a given time point, the long-term persistence of VISP, using a centralized serological HIV test, which is performed routinely worldwide for the

detection of HIV infection, in order to study factors associated with VISP, and to estimate test ratio distributions in the cohort of HIV preventive vaccine trial participants in the ANRS network.

Methods

Study design

The COHVAC cohort is the French ANRS prospective multicentre cohort, and includes healthy volunteers having received at least

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Received December 12, 2013; **Accepted** January 17, 2014; **Published** January 21, 2014

Citation: Desaint C, Durier C, Poda A, Krivine A, Simon F, et al. (2014) Long-Term Persistence of Vaccine-Induced HIV Seropositivity in Healthy Volunteers. J AIDS Clin Res 5: 275. doi:[10.4172/2155-6113.1000275](http://dx.doi.org/10.4172/2155-6113.1000275)

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one vaccine candidate injection in phase 1 or 2 ANRS trials. As the main purpose of this cohort is to study the long-term safety of HIV preventive vaccine candidates, clinical data (adverse events, medications, vital signs), HIV serology and blood samples are collected every year, over a period of 7 years. Written informed consent was obtained from each participant before enrolment. The protocol was applied in accordance with the Declaration of Helsinki and French law for biomedical research, and was approved by the "Ile-de-France III" Ethics Committee (Paris, France).

HIV vaccine candidates

Between 1992 and 2007, 16 trials were conducted, including 422 volunteers who received: recombinant envelope glycoproteins (rgp160), from 1992 to 1993, ALVAC-HIV 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 [9,12-17]. The vaccines were injected intramuscularly, except in one mucosal gp160 trial and one intradermal lipopeptide trial.

To analyze the COHVAC serological data, four groups of volunteers were defined

rgp160 group: volunteers who received recombinant glycoproteins

(rgp 160) associated with adjuvants and other vaccine candidates, namely ALVAC-HIV canarypox (vCP) vectors (ANRS VAC01/VAC05 and ANRS VAC02/VAC06 trials). The vaccine schedules for these trials are provided in Table 1.

vCP group: volunteers who received vCP alone or associated with other products, with the exception of recombinant glycoproteins (ANRS VAC03 VAC07 LIP03 VAC10 trials).

LIPO group: volunteers who received HIV-1 lipopeptides (LIPO) alone (ANRS VAC04 VAC17 VAC12 VAC16 VAC18 trials).

gp160muc group: volunteers who received recombinant glycoproteins (rgp160) by the mucosal route (ANRS VAC14).

Laboratory testing

For serum collected at the first visit of the COHVAC study, serological tests were performed using the ABBOTT ARCHITECT® HIV Ag/Ac Combo EIA test (Abbott Laboratories, Chicago, IL) on an i2000 ARCHITECT® platform, in a central laboratory at Cochin Hospital (Paris, France). This 4th generation EIA test, which can simultaneously detect the p24 antigen and anti-HIV-1/2 antibodies, is used worldwide for HIV infection screening. According to the manufacturer's recommendations, samples are considered positive if the chemiluminescence or signal-to-cut-off ratio (S/CO) is ≥ 1 ,

Trial 1	Trial 2	Yr	Vaccines	ARCHITECT									
					Ratio	Western Blot							
VAC01	VAC05	16.6	vCP125	rgp160(CFA)	vCP65	+	13.33	gp160	traces	p55	weak	p24	weak
VAC01	VAC05	16.7	vCP125	rgp160(CFA)	vCP205	+	12.58	gp160	weak	p55	weak	p18	traces
VAC01	VAC05	16.6	vCP125	rgp160(CFA)	vCP65	+	7.60	p68		p55		p18	traces
VAC01	VAC05	16.5	vCP125	rgp160(CFA)	vCP65	+	5.63			p55			
VAC01	VAC05	16.6	vCP125	rgp160(CFA)	vCP65	+	3.59	ND					
VAC01		17.7	vCP125	rgp160(alum)		+	3.02			p55	traces	p18	traces
VAC01	VAC05	16.6	vCP125	rgp160(alum)	vCP205	+	2.06			p55	traces	p18	traces
VAC01	VAC05	16.6	vCP125	rgp160(CFA)	vCP205	+	1.02	ND					
VAC01	VAC05	16.6	vCP125	rgp160(alum)	vCP205	-	0.84	ND					
VAC02		18.3	rgp160 (IFA)	peptV3		+	14.04	gp160	weak	p55	traces	p18	traces
VAC02	VAC06	16.5	rgp160 (IFA)	peptV3	vCP125	+	13.51	gp160	traces	p55	traces		
VAC02	VAC06	16.4	rgp160 (alum)		vCP65	+	13.39	gp160	traces	p55	traces		
VAC02		16.8	rgp160 (alum)			+	3.44			p55	weak	p18	traces
VAC02	VAC06	16.5	rgp160 (alum)	peptV3	vCP65	+	3.14			p55	weak	p18	traces
VAC02		16.7	rgp160 (alum)	peptV3		+	2.50	Negative					
VAC02		16.5	rgp160 (IFA)	peptV3		+	2.03			p55	traces	p18	traces
VAC02	VAC06	16.7	rgp160 (alum)	peptV3	vCP65	+	1.96	Negative					
VAC02	VAC06	16.6	rgp160 (IFA)	peptV3	vCP65	+	1.88			p55	traces	p18	traces
VAC02	VAC06	17.0	rgp160 (IFA)	peptV3	vCP125	+	1.72					p18	traces
VAC02	VAC06	16.5	rgp160 (alum)	peptV3	vCP125	+	1.68	Negative					
VAC02		16.7	rgp160 (alum)	peptV3		+	1.48	Negative					
VAC02		16.7	rgp160 (IFA)	peptV3		-	0.97	ND					
VAC02	VAC06	16.7	rgp160 (alum)		vCP65	-	0.94	ND					
VAC02	VAC06	16.6	rgp160 (alum)	peptV3	vCP125	-	0.84	ND					
VAC02	VAC06	17.4	rgp160 (IFA)	peptV3	vCP65	-	0.66	ND					
VAC02	VAC06	16.3	rgp160 (alum)		vCP65	-	0.61	ND					
VAC02	VAC06	16.6	rgp160 (IFA)	peptV3	vCP65	-	0.50	ND					
VAC02		16.8	rgp160 (alum)			-	0.32	ND					
VAC02		18.4	rgp160 (alum)	peptV3		-	0.19	ND					

Yr: time in years since 1st injection; rgp160: recombinant gp160 ; CFA: complete Freund adjuvant; alum: aluminium hydroxide; IFA: incomplete Freund adjuvant; vCP125: ALVAC-HIV canarypox vector coding for gp160; vCP65: ALVAC canarypox vector coding for rabies G protein; vCP205: ALVAC-HIV canarypox vector coding for gp120; peptV3: gp120 V3 peptide loop; ND: not done

Table 1: Serological results obtained with the ARCHITECT and Western blot assays in the rgp160 group (rgp160 alone or combined with vCP recipients).

and negative if this ratio is < 1 . No grey zone was considered. HIV-1 Western blots (New LAV Blot-1; Bio-Rad Laboratories, Hercules, CA) were performed in positive EIA samples. The Western blot interpretation was made according to the French National Authority for Health (HAS) recommendations [18].

Definition of VISP

VISP was defined in terms of ARCHITECT test positivity, regardless of Western blot results.

Statistical analysis

VISP results were analyzed according to the frequency in the different groups with their exact 95% confidence interval, and compared using the Chi-squared or Fisher tests. The ARCHITECT ratios were summarized by their median, inter-quartile range (IQR) and extreme values, and compared with nonparametric Mann-Whitney or Kruskal-Wallis tests. All statistical analyses were carried out using STATA 11.0 software.

Results

Of the 422 vaccine recipients, 296 (70%) were included in the COHVAC study (Figure 1). Among these, 293 had their serum sample tested with the ARCHITECT HIV Ag/Ac Combo. Most volunteers were male (54%). The median age at inclusion in trials was 46 years (IQR: 39-50, range: 23-55 years). The median age at inclusion in the COHVAC cohort was 53 years (IQR: 47-58, range: 26-71 years). The median duration, between injection of the first vaccine and cohort inclusion, was 6 years (IQR: 4-13, range: 2-18 years).

VISP was evidenced in 21 (7.2%) of the 293 included participants (Confidence interval (CI) 95%: 4.2%-10.7%). In the rgp160 group (n=29), after a median period of 16.6 years (range: 16.3-18.4) following

initial injection, 20 volunteers had VISP (69%; CI 95%: 51% - 86.9%). In the vCP (n=56) and gp160muc (n=29) groups, no volunteer had VISP, after a median period of 15 (range: 8-17) and 6 (range: 5-8) years, respectively. In the LIPO group (n=179), only one volunteer (0.6%) had VISP 5 years after vaccination.

The median S/CO ratio for participants with a positive ARCHITECT test (ratio ≥ 1) was 3.02 (IQR: 1.88-7.60, range: 1.02-14.04). The median S/CO ratio for participants with a negative ARCHITECT test (< 1) was 0.15, and was higher ($p < 0.00001$) in the rgp160 group (median: 0.66, IQR: 0.50-0.84, range: 0.19-0.97) than in the other groups (median ratio: 0.15; IQR: 0.12-0.19; range: 0.01-0.83). In the case of the VAC01 and VAC02 trials, the median S/CO ratios were 3.59 (range: 0.84-13.33) and 1.70 (range: 0.19-14.04), respectively, revealing an observable trend ($p = 0.08$).

Among the 21 volunteers with a positive EIA, 19 were tested using Western blot (Table 1) and faintly reactive bands were detected, mainly against Gag proteins with traces of p55 (n=13, 68.4%), and p18 (n=11, 57.9%). In the 5 volunteers with S/CO ratios above 10, p24 and p68 were reactive in 1 volunteer each, and gp160 in all 5 volunteers, as compared to 0 volunteer with S/CO ratio between 1 and 10.

Due to the absence of VISP in the gp160muc and vCP groups, and to a single case of VISP in the LIPO group, the study of predictive factors for VISP was restricted to the rgp160 group. There was no statistical relationship between VISP at inclusion in the COHVAC and gender (73% female, 67% male, $p = 1.0$), age (64% for age below 40 years; 73% for age over 40 years, $p = 0.7$) or time since injection (50%, 74% and 50% for 16, 17 and 18 years respectively, $p = 0.5$). The VISP frequencies in VAC01 and VAC02 participants included in COHVAC were 8/9 (89%) and 12/20 (60%), respectively ($p = 0.20$).

Discussion

In this cross-sectional study, it is found that nearly 17 years after receiving recombinant envelope glycoproteins (rgp160), 69% of healthy recipients had persistent VISP, detected by a centralized, routine serological testing.

This appears to be the first study evaluating long-term VISP persistence. VISP studies have in general been carried out immediately after the end of vaccine trials [5,7,8,19]. In the key study of phase 1 and phase 2a trials of the HIV Vaccine Trials Network (HVTN) [8], VISP varied across different vaccine products: 100% of gp140 protein recipients and 49% of vCP recipients developed VISP. In a previous published study including participants of ANRS vaccine trials and using local HIV testing, VISP was present in 100% of 43 volunteers at the end of their participation in VAC01 and VAC02 (rgp160 ± vCP recipients) and persisted in 34/36 (94%) and 29/35 (83%) of them, 5 and 8 years after vaccination, respectively [11]. Among those 43 volunteers, 14 volunteers were not included in our cohort, 20 volunteers were positive and 9 were negative with ARCHITECT test after a median period of 16 years after immunization. Because of dropouts and varying EIA tests over time, a cross-sectional analysis aimed at characterizing VISP with a centralized EIA test was performed here, rather than a longitudinal analysis of these data.

With the exception of the type of vaccine candidate, namely rgp160, with or without canarypox vector coding for the envelope protein (vCP125), no other factors related to VISP were found. These results reinforce previously published data, which did not reveal any relationship between VISP, age and gender [8,11]. Although it is not

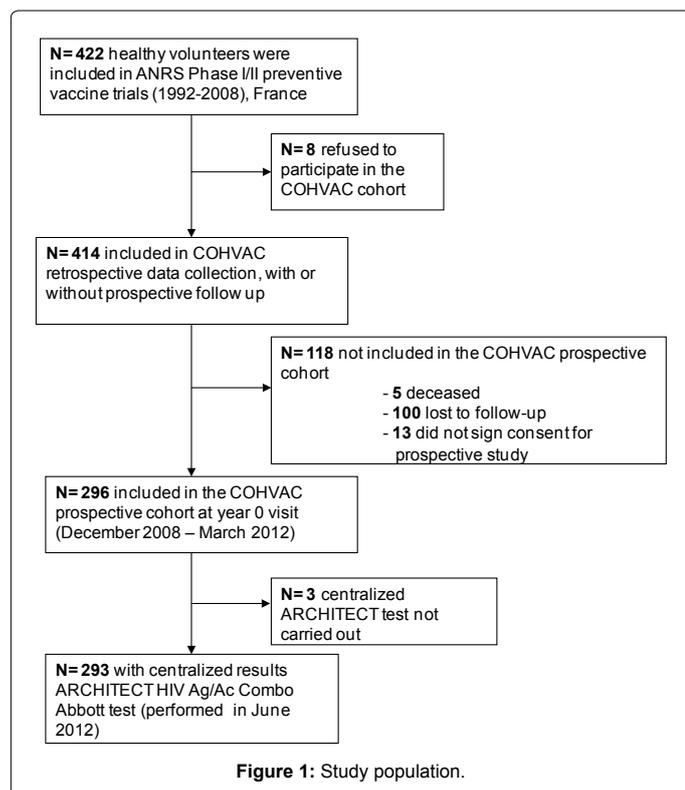


Figure 1: Study population.

significant, a trend was observed in favor of the combination of ALVAC-HIV vCP used as prime and rgp160 as boost vaccine, corresponding to the Thai RV144 regimen [4], rather than a combination of rgp160, followed by a gp120 peptide and occasionally vCP.

Among the 19 participants with VISP, tested with the Western blot assay, one had a probably positive result (gp160, p24 weak bands; first row of Table 1), four had an indeterminate result (gp160), and 13 had a negative result, as determined in accordance with the HAS recommendations [18]. In the case of probably positive or indeterminate result, the absence of a HIV risk factor and constancy or loss of bands in the Western blot assays, one year later as well as in the test results since the beginning of the vaccine trial, support the absence of any HIV infection. Only volunteers with highest ARCHITECT ratios were reactive to the gp160 band. The gp160 band in the New Lav blot 1 represents a multimer of the gp41 transmembrane, an antigen used in the ARCHITECT HIV-1 test to detect the anti gp41 antibodies [20]. This explains the association observed between the high ARCHITECT reactivity and positive gp160. Observed Western blot Gag reactivities must be considered as false positivity and unrelated to the EIA reactivity, as documented in previous studies [21,22]. This outcome explains the discrepancy between the antigens used in the vaccination, leading to anti-gp160 synthesis only, and the erratic anti-Gag reactivity.

In the participants producing a positive ARCHITECT test, the median ratio was 3.02 (IQR: 1.88-7.60 and extreme values: 1.02 and 14.04). In a study evaluating the performance of the ARCHITECT test in 10995 tested samples, the median ratio for chronically HIV-infected patients (n=3824) was 411.9 (IQR: 307.8-493.6), for false positive subjects (n=92) was 2.9 (IQR: 1.6-8.5), and the IQR interval for acute HIV-infection patient ratios was: 10.5-57.2 [23]. The ratios observed in subjects with long-term VISP are clearly low, when compared to the ratios of chronically HIV-infected patients [23-25], but are comparable with the false-positive samples. Some of these ratios overlap those corresponding to recent acute HIV infections (Table 1). As the ARCHITECT test cannot distinguish between VISP and acute HIV infections, an algorithm using more specific methods (EIA, Western blot, nucleic acid amplification testing) is thus necessary to distinguish VISP from an acute HIV infection status.

The sample size used in this study clearly restricts the conclusions that can be drawn. When analyzing the data, the various vaccine candidate doses and adjuvants, the number of doses and vaccine schedules were not taken into account, because of complex relationships between these variables. However, its findings provide valuable information, since very little long-term data has been published concerning the consequences of participation in HIV preventive vaccine trials. Moreover, long term persistence of humoral response observed in this study may lead to further characterize antibodies subclasses, neutralization properties, and specificity to explore possible cross reactivity as already described [26], which might also explain the persistence of the response for such a long period.

In conclusion, this is the first study to report on the use of ARCHITECT test ratios and the persistence of vaccine-induced seropositivity, more than 15 years following HIV envelope vaccine trials. Participants in HIV preventive vaccine trials inducing humoral immunity should be informed of the possibility of very long-term seropositivity persistence. Other technologies relevant to resource-limited settings should be evaluated, to differentiate between vaccine-induced seropositivity and a recent HIV infection. The development of new HIV vaccine candidates stimulating both cellular and humoral

immunity reinforces the need for specific diagnostic tests, in particular for participants exposed to a high risk of HIV infection.

Acknowledgments

Participating Clinical Departments: AP-HP Hôpital Cochin, CIC Vaccinologie Cochin-Pasteur, Paris (O. Launay, P. Duchet Niedziolka, L. Belarbi, B. Phung, H. Bodilis, P. Loulergue, W. Nouioua), AP-HP Hôpital Tenon, Paris (G. Pialoux, L. Slama, C. Fontaine, T. L'Yavanc, J. Chas, S. Le Nagat), AP-HP Hôpital Henri Mondor, Créteil (J-D Lelièvre, G. Melica), CHU Hôtel-Dieu, Nantes (B. Bonnet, P. Morineau Le Houssine, N. Feuillebois), Hôpital Sainte-Marguerite CISH, Marseille (I. Poizot-Martin, M-P. Drogoul-Vey, A. Menard, E. Peyrouse, N. Cloarec, O. Faucher), Hôpital Purpan, Toulouse (L. Cuzin, M. Chauveau)

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Vaccine Research Institute (VRI): Y. Lévy, J-D. Lelièvre, A. Bouakane, V. Rieux

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Healthy volunteers for the generous gift of their time.

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Citation: Desaint C, Durier C, Poda A, Krivine A, Simon F, et al. (2014) Long-Term Persistence of Vaccine-Induced HIV Seropositivity in Healthy Volunteers. *J AIDS Clin Res* 5: 275. doi:[10.4172/2155-6113.1000275](https://doi.org/10.4172/2155-6113.1000275)

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