DURABILITY OF THE IMMUNE RESPONSE AFTER VACCINATION WITH TWO DOSES OF H1N1v 2009 VACCINE FORMULATED WITH AND WITHOUT AS03$_A$-ADJUVANT IN HIV$^+$ ADULTS

ANRS 151 Randomized HIFLUVAC Trial

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ABSTRACT

Background
We previously reported that the AS03$_A$-adjuvanted H1N1v vaccine yielded a higher immune response than the non adjuvanted one in HIV-1 infected adults with no impact on HIV infection. However, there are no published data on durability of H1N1 antibody levels and seroprotection rates.

Methods
In a prospective, multicenter, patient-blinded trial, stratified according to antiretroviral treatment (ART) or not, started in 2009, 306 HIV-infected adults (median age 47 years, median CD4 536 cell/µl, 76% viral load <50 cp/ml) were randomized to receive 2 doses of either AS03$_A$-adjuvanted H1N1v vaccine containing 3.75µg haemagglutinin (HA) (group A, n=154) or non-adjuvanted H1N1v vaccine containing 15µg HA (group B, n=152) 21 days apart. Haemagglutination-inhibition (HI) antibody responses were analyzed on Day 0, 21 days after each vaccination and on Days 182 and 364. We report here the durability of the immune response until 12 months after vaccination as of November 10, 2010.

Results
Pre-vaccination HI titers of 1:40 or greater (level considered to be protective) were found in 9% of patients; the geometric mean titer (GMT) for HI antibodies was 8.3 (95% confidence interval [CI]: 7.5-9.1). Twenty-one days after the second vaccination, 98.6% (141/143) of patients of the group A and 92.1% (128/139) of the group B had seroprotective HI titers (p=0.018); GMTs for HI antibodies were 381.9 (95% CI: 329.0-443.3) in Group A and 171.1 (95% CI: 141.9-206.3) in Group B. The proportion of patients retaining putatively seroprotective titers 6 and 12 months after two doses of vaccine was greater in adjuvanted vaccine recipients: 83.7% (118/141) and 71.5% (93/130) in Group A, and 59.9% (82/137) and 47.9% (57/119) in Group B, respectively. GMTs were higher in Group A at 6 and 12 months: 82.0 (95% CI: 68.4-98.3) and 61.9 (95% CI: 51.2-74.9) vs. 47.1 (95% CI: 37.7-58.8) and 37.5 (95% CI: 29.2-48.1) in Group B. In a multivariate analysis, the predictors of persistence of seroprotection 6 and 12 months after vaccination were the AS03$_A$-adjuvanted H1N1v vaccine (Odds Ratio [OR]=3.7 P=.00001, OR=3.0 P=.00009) and use of ART (OR=2.0 P=0.025, OR=1.9 P=0.048).

Conclusions
In HIV-1 infected adults, the AS03$_A$-adjuvanted H1N1v 2009 vaccine yielded a higher and more durable immune response than the non adjuvanted one. Altogether, two-dose H1N1v vaccination schedule maintained HI titers of 1:40 or greater in 60% (95% CI: 54-66%) of patients one year later.

BACKGROUND AND OBJECTIVE

We previously reported that the **AS03$_A$-adjuvanted H1N1v vaccine** yielded a higher immune response than the **non adjuvanted H1N1v vaccine** in HIV-1 infected adults with no impact on HIV infection *(Launay O, Desaint C, Durier C, et al. J Infect Dis, in press).*
However, there are no published data on durability of H1N1 antibody levels and seroprotection rates.
We report here on the antibody responses up to one year after vaccination with two doses of H1N1 vaccine adjuvanted or not with AS03$_A$.

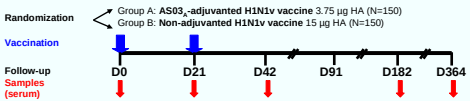
METHODS

Study vaccine

Monovalent A/H1N1v inactivated, split-virion vaccine (FLU D-PAN H1N1 [A/California/7/2009 (H1N1)v]) manufactured by GlaxoSmithKline (GSK) Biologicals (Dresden, Germany).
➢ AS03$_A$-adjuvanted H1N1v was formulated with 3.75 µg haemagglutinin (HA) and AS03$_A$, a tocopherol oil-in-water emulsion adjuvant system manufactured by GSK Biologicals.
➢ Non-adjuvanted vaccine was formulated with 15 µg HA.
The H1N1v vaccine was in multidose vials and injected intra-muscularly, with 0.5 mL of antigen suspension mixed or not with AS03$_A$ adjuvant emulsion.

Study design and participants

• Randomized (1:1), patient-blinded trial, stratified according to HAART.
• Participants were **HIV-1-infected adult patients**, either receiving HAART for at least 6 months (HIV viral load <50 copies/mL) or without ARV therapy for at least 6 months and with no expected indication to start HAART in the following 3 months.
Exclusion criteria included pregnancy, immune-modulatory drugs (IFNalpha, IL-2..), thrombopenia, febrile episode within one week prior to vaccination, opportunistic infection treated for less than 1 month, clinically or virologically documented influenza in the last 6 months, history of auto-immune disease, child C cirrhosis, solid organ transplant recipient, other immunization within 3 weeks prior to inclusion or planned until the 2nd vaccination. All participants provided written informed consent.



• Serum haemagglutination inhibition (HI) antibodies have been analyzed by personnel blinded to vaccine allocation, in a validated micro-titre HI test using chicken erythrocytes with the A/California/7/2009 (H1N1)v strain as antigen. Individual results are geometric means of duplicates.
• Sample size was calculated on the basis of fulfilment of EMEA (CHMP) and FDA criteria for the standard HI endpoints (seroprotection, seroconversion, and seroconversion factor – see Immune responses table).
• As planned, analyses were descriptive and presented vaccinated and tested patients for immunogenicity (preliminary, as of November 10, 2010) ; 95% confidence intervals (CI) for rates were Exact (Clopper-Pearson) confidence intervals. Logistic regressions were used to determine the factors associated with HI titers ≥ 1:40.

RESULTS

Demographic and clinical characteristics

	Group A AS03$_A$-adjuvanted H1N1v vaccine (3.75 µg HA) N=155	Group B Non-adjuvanted H1N1v vaccine (15 µg HA) N=151
Sex: female, n (%)	23 (15)	36 (24)
Age: median (IQR)	46.5 (38.6-54.0)	47.3 (40.2-53.6)
CDC stage C, n (%)	40 (26)	39 (26)
Smoker, n (%)	61 (39)	50 (33)
HCV and/or HBV co-infection, n (%) AcHCV+ and/or AgHBs+	23 (15)	16 (11)
Nadir CD4 /mm³, median (IQR)	240 (107-369)	204 (95-371)
Baseline CD4 /mm³, median (IQR)	522 (378-752)	551 (428-702)
ARV Treatment		
with HAART, n (%)	120 (77)	117 (77)
w/o HAART, n (%)	35 (23)	34 (23)
Baseline HIV RNA		
<50 cp/mL, n (%)	119 (77)	112 (74)
w/o HAART, log10 cp/mL, median (IQR)	13372 (1524-46081)	8306 (3850-29048)
Seasonal influenza vaccine prior to H1N1v vaccination, n (%)	39 (33)	39 (26)

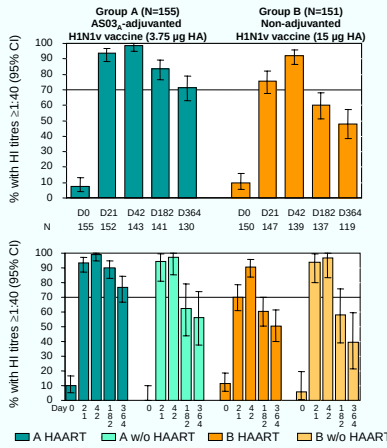
Immune responses : HI antibodies against A/California/7/2009 (H1N1)v

	Group A AS03$_A$-adjuvanted H1N1v vaccine (3.75 µg HA)			Group B Non-adjuvanted H1N1v vaccine (15 µg HA)		
	HAART	w/o HAART	All	HAART	w/o HAART	All
PRE-VACCINATION AT DAY 0						
No. of subjects	120	35	155	116	34	150
Geometric mean titre (GMT) (95% CI)	9.2 (7.7-10.9)	6.4 (5.3-7.7)	**8.5 (7.3-9.8)**	8.6 (7.3-10.0)	6.7 (5.4-8.4)	**8.1 (7.1-9.2)**
Seroprotection (titre ≥ 1:40) (95% CI)	10.0 (5.3-16.8)	0.0 (0.0-10.0)	**7.7 (4.1-13.1)**	11.2 (6.1-18.4)	5.9 (0.7-19.7)	**10.0 (5.7-16.0)**
POST-DOSE 2 AT DAY 42						
No. of subjects	108	35	143	108	31	139
Geometric mean titre (95% CI)	424.4 (358.3-502.7)	275.7 (203.8-373.0)	**381.9 (329.0-443.3)**	164.1 (131.4-205.0)	197.8 (141.1-277.3)	**171.1 (141.9-206.3)**
Seroprotection (titre ≥ 1:40) (%) (95% CI)	99.1 (95.0-100.0)	97.1 (85.1-99.9)	**98.6 (95.0-99.8)**	90.7 (83.6-95.5)	96.8 (83.3-99.9)	**92.1 (86.3-96.0)**
Seroconversion rate (%) (95% CI)	96.3 (90.8-99.9)	97.1 (85.1-99.9)	**96.5 (92.0-98.9)**	85.2 (77.1-91.3)	93.6 (78.6-99.2)	**87.1 (80.3-92.1)**
Geometric mean fold rise (seroconversion factor) (95% CI)	46.3 (36.6-58.6)	43.1 (31.6-58.8)	**45.5 (37.6-55.1)**	19.5 (15.5-24.5)	28.6 (20.9-39.2)	**21.2 (17.5-25.7)**
POST-DOSE 2 AT DAY 182						
No. of subjects	109	32	141	106	31	137
Geometric mean titre (95% CI)	92.3 (76.5-111.3)	54.7 (34.0-88.0)	**82.0 (68.4-98.3)**	47.8 (36.9-62.0)	44.7 (28.5-70.1)	**47.1 (37.7-58.8)**
Seroprotection (titre ≥ 1:40) (%) (95% CI)	89.9 (82.7-94.9)	62.5 (43.7-78.9)	**83.7 (76.5-89.4)**	60.4 (50.4-69.8)	58.1 (39.1-75.5)	**59.9 (51.1-68.1**
POST-DOSE 2 AT DAY 364						
No. of subjects	98	32	130	91	28	119
Geometric mean titre (95% CI)	71.9 (58.0-89.1)	41.7 (27.6-63.1)	**61.9 (51.2-74.9)**	40.5 (30.0-54.7)	31.9 (20.0-50.8)	**37.5 (29.2-48.1)**
Seroprotection (titre ≥ 1:40) (%) (95% CI)	76.5 (66.9-84.5)	56.3 (37.7-73.6)	**71.5 (63.0-79.1)**	50.6 (39.9-61.2)	39.3 (21.5-59.4)	**47.9 (38.7-57.3)**

Seroprotection rate (SPR): percentage of patients with HI antibody titre ≥ 1:40.
Seroconversion rate (SCR): percentage of patients with prevaccination HI antibody titre <1:10 and post-vaccination titre ≥ 1:40, or a prevaccination titre ≥ 1:10 and at least a fourfold increase in post-vaccination titre.
Seroconversion factor (SCF): geometric mean of the within-subject ratios of the reciprocal titre to day 0.

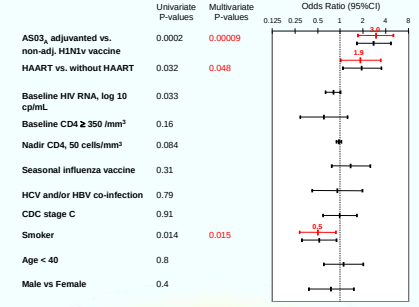
CHMP criteria (<60 years of age)	
SPR	> 70%
SCR	> 40%
SCF	> 2.5

Pre and post-vaccination HI titres ≥ 1:40



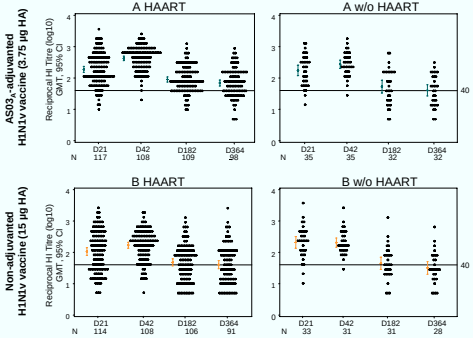
Predictors of seroprotection (HI titres ≥1:40) were:
• **at day 21** (post-dose 1) AS03$_A$-adjuvanted H1N1v vaccine (OR=5.33, P<.00001) and HCV or HBV co-infection (OR=0.26, P=0.0023)
• **at day 42** (post-dose 2) AS03$_A$-adjuvanted H1N1v vaccine (OR=6.52, P=0.018).

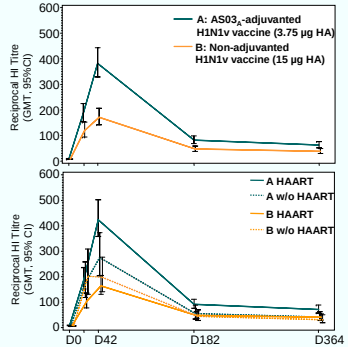
Univariate and multivariate analysis of predictive factors for Persistence of HI titres ≥1:40 at day 364



Similar results obtained for persistence of HI titres ≥1:40 **at day 182:** predictors of persistence of seroprotection 6 months after vaccination were the AS03$_A$-adjuvanted H1N1v vaccine (OR=3.7, P-value=.00001) and use of ART (OR=2.0, P=0.025).

HI antibodies against A/California/7/2009 (H1N1)v





CONCLUSIONS

• In HIV-1 infected adults, the AS03$_A$-adjuvanted H1N1v 2009 vaccine yielded a higher and more durable immune response than the non adjuvanted one.
• Altogether, two-dose H1N1v vaccination schedule maintained HI titers of 1:40 or greater in 60% (95% CI: 54-66%) of patients one year later (71.5% et 47.9% with AS03$_A$-adjuvanted and non-adjuvanted vaccine, respectively).

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