

# Randomized Trial Comparing a Three Dose Regimen to a Standard Two Dose Regimen of Hepatitis A Vaccine in HIV-Infected Adult Patients with CD4+ T cells between 200 and 500 per mm<sup>3</sup> (HEPAVAC Study).

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## ABSTRACT

**Background** HIV-infected patients have weak responses to vaccine and may require immunization regimens. The immunogenicity and safety of 3 doses versus 2 doses hepatitis A vaccine were compared in HIV-infected patients.

**Methods** In a prospective open trial, 93 HAV seronegative HIV-infected patients 21 to 55 years of age, CD4 T cells between 200 and 500 per mm<sup>3</sup> and plasma viral load  $\leq$  50,000 copies/ml were randomized to receive either 3 hepatitis A vaccine doses (1440 ELISA units) at weeks 0, 4 and 24, or 2 vaccine doses 24 weeks apart. Anti-HAV antibodies titers were measured 4 weeks after each vaccination using a quantitative immunoenzymatic test (Diasorin). Primary endpoint was the percentage of patients with seroconversion (antibodies titers  $\geq$  20 mIU/ml) 4 weeks after the last vaccine dose (week 28). Univariate and multivariate analyses were performed to determine predictive factors of response to vaccine administration.

**Results** In an intent-to-treat analysis, the percentage of seroconversion at week 28 was 71% in the 3 vaccine doses and 58% in the 2 vaccine doses (p=0.20). At week 28, the geometric mean HAV antibody titer was 290 mIU/ml in the 3 doses group, and 125 mIU/ml in the 2 doses group (p=0.08). A statistically significant higher seroconversion rate was associated with 3 doses comparing with standard 2 doses for patients with CD4+ T cell counts  $\leq$  350 cells/mm<sup>3</sup> (73% versus 39%; p=0.02). After the first dose of vaccine, seroconversion was observed in only 42% of patients. There were no serious adverse events associated with the vaccine. Multivariate analysis showed no vaccine dose effect, but indicated that smoking was an independent predictor of non response to vaccine (OR=2.78, 95%CI 1.03-7.69; p=0.02).

**Conclusions** In HIV-infected adults with CD4+ T cells between 200 and 500 per mm<sup>3</sup>, immunogenicity of HAV vaccine is low with only 58% of seroconversion in the 2-dose immunization regimen. This is much lower than reported rates of 100%, in healthy adults. A third vaccine dose was safe and increased the antibody titers and the rate of seroconversion in patients with CD4+ T cell below 350 per mm<sup>3</sup>. These results suggest that anti-HAV antibodies titers should be measured after immunization even in those with CD4 cells above 350/mm<sup>3</sup> and that an increase in immunizations may be warranted in this population.

## BACKGROUND

- Susceptible HIV-infected patients at increased risk for Hepatitis A Virus (HAV) or with chronic liver disease should be vaccinated against HAV.
- Immune response to HAV vaccine is lower in HIV-infected patients compared to normal population and many questions remained, in this population, concerning the best vaccination schedule to be used.
- Previous study showed that an increase in immunizations may be warranted in this population.

## OBJECTIVES

- To compare immunogenicity of a 3 doses regimen versus standard 2 doses regimen of HAV vaccine in HIV-infected adult patients with CD4+ T cells between 200 and 500 per mm<sup>3</sup>.
- To assess safety of the 2 vaccination schedules.
- To determine the predictive factors of response to HAV vaccine administration.

## METHODS

### Patients recruitment:

- Multicenter open trial in 7 French hospitals
- HIV-infected patients were randomized in 2 groups:
  - > 3 doses group** > received 3 IM injections (HAVRIX® 1440 IU) at weeks 0, 4 and 24.
  - > 2 doses group** > received 2 IM injections (HAVRIX® 1440 IU) at weeks 0 and 24.
- Randomization was centralized and stratified on baseline CD4 cell count (200-349 and 350-500/mm<sup>3</sup>) and HCV or HBV co-infection.
- Main inclusion criteria:
  - CD4+ T between 200 and 500 cells/mm<sup>3</sup>
  - HIV-1 RNA  $<$  50,000 cp/ml
  - 18 and 55 years old

- Main non inclusion criteria:
  - immunized to VHA (IgG)
  - corticosteroids, immunosuppressive or immunomodulator therapy

### Laboratory methods:

Anti-HAV antibody titers were measured in serum 4 weeks after each immunization using a quantitative immunoenzymatic test (Diasorin) and performed centrally and blinded to the intervention assignment, after all the patients had completed W28 visit.

### Statistical methods:

- Primary endpoint** : Percentage of patients with seroconversion (HAV antibodies titers  $\geq$  20 mIU/ml) 4 weeks after the last vaccine dose (week 28).
- Statistical analysis was realized on **intention to treat**.
- Primary analysis** : patients who had no seroconversion data at week 28 were considered as non-responders.
- Sensitivity analyses** : Last Observation Carried Forward (LOCF) analysis was used. For this analysis, missing HAV antibodies titers were replaced by last measured previous titer.
- The frequency of seroconversion and geometric mean HAV antibodies titers (GMT) and their 95% confidence intervals were determined globally and by CD4 cell count strata.
- Seroconversion comparisons between groups were tested by 2-tailed chi-2 test.
- Logistic regression analysis was used to determine the factors associated with a seroconversion. Univariate analysis was performed for vaccination group, sex, age, tobacco smoking, HCV or HIV infection, HIV exposure category, AIDS status (CDC C), antiretroviral treatment, baseline CD4 cell count, nadir of CD4 and HIV-1 RNA levels. All the variables with a p-value below 0.2 in univariate analysis were included in the multivariate model.

## RESULTS

### Population included in the study:

- Inclusion began in June 2003 and finished in May 2005.

Figure 1 : Flow chart (Enrollment, allocation, follow-up, analysis)

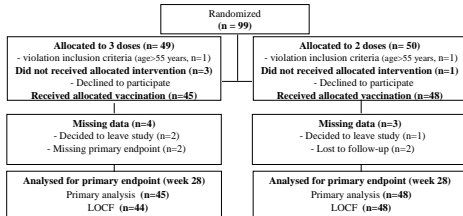


Table 1 a : Characteristics of patients at baseline (week 0).

		Received 3 injections (n=45)	Received 2 injections (n=48)
Sex (n (%))	Men	38 (84.4)	39 (81.3)
Age (years)	Median (IQR)	39.0 (33.5-41.6)	37.2 (34-42.9)
AIDS status (CDC c) (n (%))		11 (24.4)	11 (22.9)
HIV transmission group (n (%))	Homosexuals	29 (64.5)	29 (60.5)
	Heterosexuals	11 (24.4)	11 (22.9)
	IV drug users	4 (8.9)	4 (8.3)
	Others	1 (2.2)	4 (8.3)
HIV diagnosis (years)	Median (IQR)	8.8 (4.3-14.9)	9.9 (4.9-14.3)
Baseline CD4 cell count/mm <sup>3</sup> (n (%))		22 (48.9)	23 (47.9)
Nadir CD4 cell count/mm <sup>3</sup>	Median (IQR)	165 (98-282)	203 (116-310)
Antiretroviral therapy (n (%))		35 (77.8)	36 (75.0)
Viral load $<$ 50 copies/ml (n (%))		24 (53.3)	27 (56.2)
Tobacco smoking	Smokers	19 (42.2)	17 (35.4)
Positive HCV or HBV infection (n (%))		6 (13.3)	8 (16.7)

Table 1 b : Trial characteristics

Number of injections received (n (%))	1 injection	2 (4,4)	2 (4,2)
	2 injections	1 (2,2)	45 (93,7)
	3 injections	42 (93,4)	1 (2,1)

### Immunogenicity at W28 : seroconversion rates and HAV antibodies titers

- Percentage of seroconversion was 71% in the 3 vaccine doses group, 58% in the 2 vaccine doses group (p=0.20, Fig 2)
- In patients with CD4+ T cell count  $<$  350 cells/mm<sup>3</sup>, percentage of seroconversion was higher in the 3 doses group than in the 2 doses group, 72.7% versus 39.1% (p=0.02).
- The geometric mean HAV antibody titers was 290 mIU/ml in the 3 doses group, 125 mIU/ml in the 2 doses group (p=0.08).

Figure 2 : Seroconversion rate at week 28 (Primary analysis)

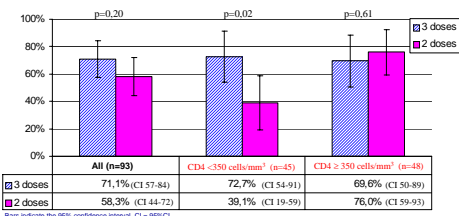
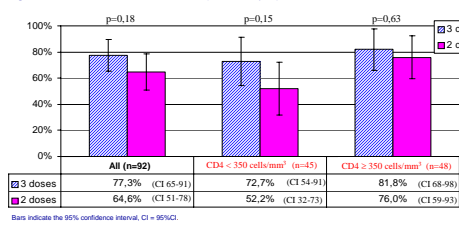


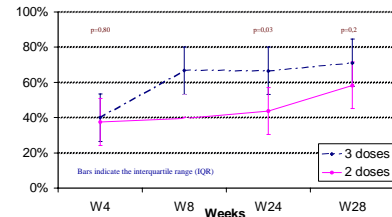
Figure 3 : Seroconversion rate at week 28 (LOCF analysis)



### Immunogenicity: Evolution of seroconversion rate

- Seroconversion was observed in only 42% of patients after one dose of vaccine (Fig 4).
- The second dose leads to an increase of the seroconversion rate, that may be of interest in a high risk population.

Figure 4 : Evolution of seroconversion rate



### Safety and predictor of the immune response:

- No serious adverse event occurred. The third injection had no deleterious effect on CD4+T cells or on HIV-1 RNA (Fig 5 and 6).
- Only smoking appeared to be an independent predictor of response to vaccine (p=0.02, Table 2).

Figure 5 : Evolution of CD4 cell count

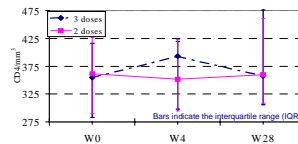


Figure 6 : Patients with viral load  $<$  50 copies/ml

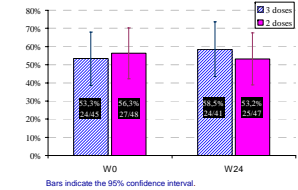


Table 2 : Factors associated with HAV vaccine response (Multivariate analysis)

Groups	n	OR [95% CI]	p
2 doses	45	1 (ref)	
3 doses	48	2.00 [0.81 ; 5.00]	0.13
CD4			
$<$ 350 cells/mm <sup>3</sup>	45	1 (ref)	
$\geq$ 350 cells/mm <sup>3</sup>	48	2.12 [0.86 ; 5.24]	0.10
Tobacco			
Yes	36	1 (ref)	
No	57	2.94 [1.18 ; 7.37]	0.02

## CONCLUSIONS

- Immunogenicity of HAV vaccine is low in HIV-infected patients with CD4+T cells between 200 and 500 per mm<sup>3</sup>
- A third dose is safe and increases the anti-HAV Ab titers and the percentage of seroconversion in patients with CD4+T cells below 350 per mm<sup>3</sup>
- HAV antibodies Ab titers should be measured after 2 immunizations and additional vaccinations proposed to increase protection in HIV infected patients

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