701

Revaccinating HIV+ Adults with Double vs Standard HBV regimen. ANRS HB04 B-BOOST trial

David Rey[1], Cécilie Dufour[2], Marie-Josée Wendling[3], Patrick Miailhes[4], Philippe Sogni[5], Georges Haour[2], Marie-Louise Michel[6], Lionel Piroth[7], Odile Launay[8], Fabrice Carrat[2], and the ANRS HB04 B-BOOST study group

1 Center for HIV infection care, CHU Strasbourg; 2 INSERM UMR-S1136, Université Pierre et Marie Curie, Paris; 3 Virology Laboratory, CHU Strasbourg; 4 Infectious and Tropical Diseases Department, CHU Lyon
5 Hepatology Department, Hôpital Cochin, Paris; 6 Institut Pasteur, Paris; 7 Infectious and Tropical Diseases Department, CHU Dijon; 8 CIC Vaccinologie, Hôpital Cochin, Paris, France

SEATTLE, WASHINGTON - February 23-26, 2015

Contact: david.rey@chru-strasbourg.fr

ABSTRACT

Background:
Immune response to standard hepatitis B (HBV) vaccination is decreased in HIV-infected patients, and it has been recently shown that a double dose HBV primary vaccination regimen improved serological response. However, the immunogenicity of this regimen in non responders to a previous vaccination is unknown.
Methods:
In an open-label, multicentre, 1:1 parallel groups randomized clinical trial, stratified according to CD4 cell count (200-349, and > 350 cells/µl), 411 HIV-infected adults, CD4 T cells ≥ 200/µl, and previously vaccinated against HBV, without HBV markers, received a booster dose (20 µg) of HBV vaccine. 178 of them who did not respond to the boost were randomized to receive HBV vaccination with either 3 intramuscular (IM) standard doses (20 µg, group A, n=90), or 3 IM double doses (40 µg, group B, n=88) at weeks 0, 4 and 24. Subjects with anti-HBs ≥ 10 mUI/mL and ≥ 100 mUI/mL at week 28 were defined as responders (main endpoint) and high responders, respectively.
Results:
The median age of the population was 44 years (IQR 40-51); 78% were male; the median CD4 cell count was 512 cells/µl (IQR 424-682); 71% had plasma viral load < 50 copies/ml. In an intent-to-treat analysis (missing = failures), the percentage of responders and high responders were 67% and 26% in group A, 74% and 47% in group B (P=.33 and P=.002). At week 28, the geometric mean titre of anti-HBs were 20 and 60 mUI/mL in group A and B respectively (P=.0004). BMI was the only factor associated with response to vaccination (>=25 vs <25, odds-ratio=2.42; 95%CI (1.1-5.3) P=.028). Among responders at week 28, 43% and 64% in group A and B respectively, had anti-HBs ≥ 10 mUI/mL at week 72 (p=.0069), and geometric mean titre of anti-HBs were 11 and 35 mUI/mL (p=.0016) in group A and B at week 72. There were two serious adverse events associated with the vaccine (1 in each group): exacerbation of psoriasis and severe headaches. Local reactions occurred in 5% of patients in group A versus 15% in group B (P=.02).
Conclusion:
In HIV-1 infected adults who did not respond to a standard dose HBV vaccination, a double-dose re-vaccination regimen does not increase the response rate but provides higher level of anti-HBs titre, with longer durability, compared with a standard re-vaccination regimen.

INTRODUCTION

- Hepatitis B virus (HBV) immunization is highly recommended in patients infected with HIV-1 and negative HBV serological markers
- Immunogenicity of hepatitis B vaccine is lower in HIV-infected adults compared to HIV-negative healthy adults (1)
- It has been shown that a 4 intramuscular double-dose regimen improved serological response in adults with HIV infection, who were not previously vaccinated, and with CD4 cell counts > 200 cells/µL (2)
- We therefore conducted a randomized multicenter study to compare the immunogenicity and safety of a reinforce vaccination protocol (3 double-dose IM injections) with a standard HBV vaccine schedule, in **non responders to previous vaccination**.

MATERIAL and METHODS (1)

- Multicenter, randomized, open label trial conducted in 53 French centers
- Inserm-ANRS was the sponsor of the trial, conducted with the support of Sanofi-Pasteur
- Main inclusion criteria:
  - HIV-1 infected patients > 18 years
  - Previously vaccinated for hepatitis B: 2 to 4 injections of a 20 µg hepatitis B vaccine, whatever the date
  - And non responders to vaccination: negative HBV markers (HBs antigen, anti-HBs Ab, anti-HBc Ab) in the 12 months preceding inclusion
  - CD4 cell count > 200/µL at screening
  - For treated patients: unchanged ARV combination for the last 2 months (if CD4 cell count < 350/µL, ARV treatment for the last 6 months combined to undetectable plasma HIV RNA was required)
  - For untreated patients: plasma HIV RNA < 10^5 copies/mL
  - Negative pregnancy test at screening and inclusion visit for women
- Main non inclusion criteria
  - History of hepatitis B vaccination with a double dose (40 µg)
  - Acute cytolysis in the last 3 months
  - Any other vaccination in the month preceding inclusion
  - Ongoing opportunistic infection or evolutive cancer
  - PT < 50% or platelets < 50 000/µL
  - Intolerance to any component of hepatitis B vaccine
  - Immunosuppressive or immunomodulating treatment in the previous 6 months
  - Splenectomy, decompensated cirrhosis, renal insuffisiency,
  - Other imunocompromised condition not related to HIV

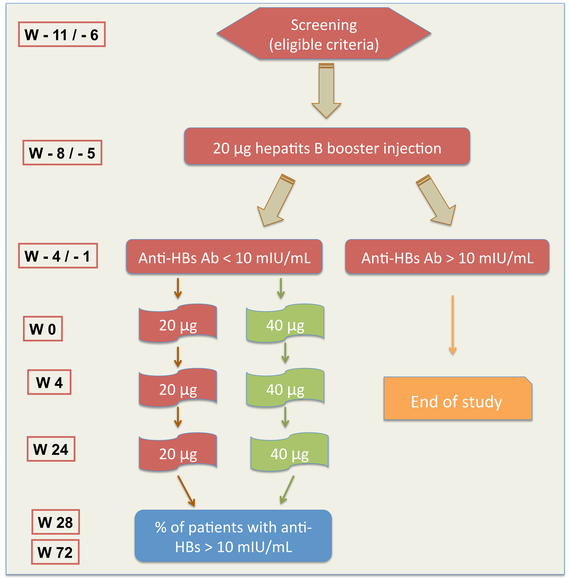
REFERENCES

1) Fonseca MO, et al. *Vaccine*. 2005;23(22):2902-2908.
2) Launay O, et al. *JAMA*,2011; 305:1432-1440 .
3) Rowley K, et al. *J Infect* 2014;:98-99.
4) Wilkins E, et al. *HIV Med* 2013;14(suppl4):1-71.

MATERIAL and METHODS (2)

- Randomization was stratified according to baseline CD4 cell count (200-349 cells/µL vs > 350 cells/µL).
- Diary cards specifying a fixed list of local and general reactions were provided
- The quantification of anti-HBs titers on serum samples was performed in a central laboratory (Laboratoire de Virologie, Hôpitaux Universitaires, Strasbourg, France) using a standardized chemiluminescent assay (Abbott Architect Anti-HBs; Abbott Ireland Diagnostics Division).
- Primary end-point:
  - percentage of responders (patients with anti-HBs titers ≥ 10 mIU/mL) 4 weeks after the last planned vaccination (week 28)
- Other prespecified immunological efficacy endpoints :
  - percentage of high-level responders (patients with anti-HBs titers ≥ 100 mIU/mL) at week 28
  - percentage of patients with anti-HBs titers of at least 10 mIU/mL at week 72 (durability of response),
  - anti-HBs geometric mean titers at weeks 28 and 72
- Other secondary endpoints:
  - proportion and intensity of general and local adverse events
  - assessment of predictive factors associated with response to vaccination

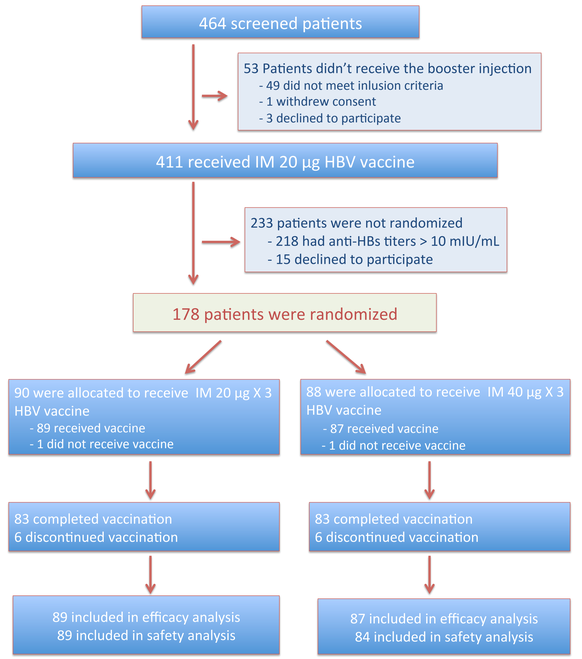
TRIAL DESIGN



STATISTICAL ANALYSIS

- Our trial was designed to have 80% power to detect a difference of 18% (36% vs 18%) of responders between IM 40 x 3 and IM 20 x 3 groups. 90 patients had to be enrolled in each group.
- The modified intention-to-treat analysis population data set was defined as all patients receiving at least 1 dose of vaccine after randomization (n=176). The same modified intention-to-treat analysis population data set was considered for primary and secondary analysis :
  - in the primary efficacy analyses, patients who missed the follow-up visit at week 28 were considered as non-responders.
  - in secondary analyses: for % of responders and high-level responders, as well as analysis of predictive covariates for response, we used the last observation carried forward to handle missing titers measurements before or at week 28; while missing titers measurements at week 72 were considered as non-response.
- A linear mixed model for repeated measurements was used to estimate the dynamic of the Geometric Mean of the anti-HBs titer,
- All patients with at least one dose of vaccine after randomization and 1 postvaccination safety measure (n=173) were included in the safety analysis.
- Cochran-Mantel Haenszel test was used with stratification on CD4 cell count at baseline to compare percentage of responders between the IM40 x 3 and the IM20 x 3 groups.
- Logistic regression analysis were used to identify predictive covariates for response. Covariates with P <.25 in the likelihood-ratio test in univariate analyses were included in multivariate model.

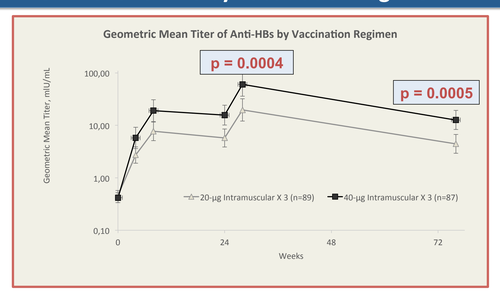
Participants flow in the ANRS HB04 B-BOOST trial



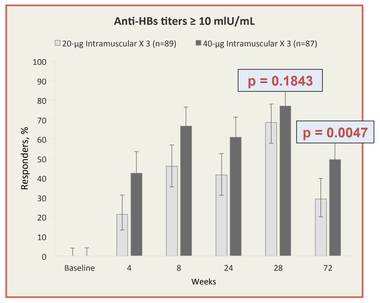
Demographic and clinical characteristics of patients by vaccination regimen

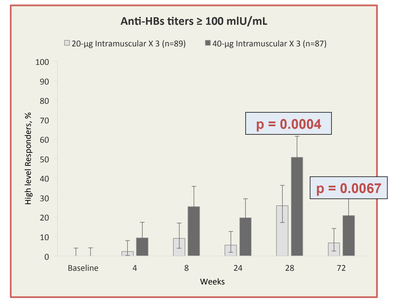
Characteristics	Recombinant HBV Vaccination Regimen	
	IM 20 x 3 (n = 90)	IM 40 x 3 (n = 88)
Women – no (%)	15 (17)	24 (27)
Age, median (range), y	44 (27-71)	44 (24-77)
BMI, median (range)	23 (14-37)	23 (17-42)
Active smoking – no (%)	30 (34)	30 (34)
Excessive alcohol use – no (%)	12 (13)	4 (5)
Anti-HCV antibodies – no (%)	5 (6)	3 (3)
Time elapsed since HIV diagnosis, median (range), y	9 (0.8-25)	8.7 (1.1-25.4)
CDC stage C – no (%)	13 (14)	13 (15)
Nadir CD4 cell count, median (range), cells/µL	254 (3-635)	207 (5-815)
Antiretroviral therapy – no (%)	77 (87)	76 (86)
Baseline CD4 cell count, median (range), cells/µL	507 (249-1210)	528 (257-1378)
CD4 cell count <=350 cells/µL – no (%)	11 (12)	9 (10)
HIV-RNA level < 50 copies/mL – no (%)	66 (74)	61 (69)

GMT of anti-HBs by vaccination regimen



Percentage of responders and high level responders by vaccination regimen





Predictive factors for response at W28

Factors	No of responders / no of participants (%)	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value
BMI, per unit increase		1.12 (1.02-1.22)	0.0077	1.10 (1.00-1.21)	0.0512
CDC stage C vs A or B	23/26 (88) vs 105/150 (70)	3.29 (0.94-11.5)	0.0360	2.82 (0.78-10.22)	0.1152
Women vs men	32/39 (82) vs 96/137 (70)	1.95 (0.8-4.78)	0.1261	1.51 (0.57-4.04)	0.4078
Active smoking vs no	38/58 (66) vs 89/117 (76)	0.6 (0.3-1.19)	0.1451	0.76 (0.36-1.63)	0.4814
Anti-HCV antibodies vs no	4/8 (50) vs 124/168 (74)	0.35 (0.09-1.48)	0.1624	0.45 (0.08-2.48)	0.3602
IM 40 x 3 vs IM 20 x 3	67/87 (77) vs 61/89 (69)	1.54 (0.79-3.01)	0.2062	1.39 (0.69-2.84)	0.3598
Age, per 10-y increase		0.81 (0.57-1.16)	0.2482	0.98 (0.94-1.01)	0.1992

Local and systemic adverse events

	IM 20 x 3 (n = 89)	IM 40 X 3 (n = 84)	Fisher exact P value
Patients with ≥ 1 adverse event (clinical or laboratory abnormalities), highest grade			
all	75 (84)	70 (83)	1
grade 1	27 (30)	34 (40)	0.5635
grade 2	40 (45)	32 (38)	
grade 3	5 (6)	3 (4)	
grade 4	3 (3)	1 (1)	
Systemic adverse events			
all	67 (75)	55 (65)	0.1834
blood pressure fluctuation	11 (12)	8 (10)	0.6308
diarrhoea	5 (6)	4 (5)	1
hypertension	5 (6)	0 (0)	0.0594
Local adverse events			
all	4 (4)	13 (15)	0.0204
pain	3 (3)	6 (7)	0.3189
Laboratory abnormalities			
all	35 (39)	34 (40)	1
hypertransaminasemia	19 (21)	19 (23)	0.8563
leucopenia	18 (20)	19 (23)	0.7149
HIV related adverse events			
all	4 (4)	5 (6)	0.7413
Serious adverse events	6 (7)	3 (4)	0.4978

CONCLUSION and DISCUSSION

- 1) 218/411 (53%) patients responded to a booster 20 µg dose, a high proportion which was unexpected.
- 2) among true non responders to past standard vaccination, 69-77% of these HIV-infected subjects responded to revaccination at week 28, but without difference according to standard or double dose regimen (in contrast to non-vaccinated patients from HB03 trial : 82% vs 65%, but double dose was administered 4 times (2)).
- 3) however, double dose vaccination induced a better high-level response (51% versus 26%), and a higher geometric mean titer of anti-HBs at week 28. Durability of response (W72) was also increased after double dose vaccination, in proportion of responders as well as in anti-HBs level (although the latter was rather low).

➔ ***HBVaxPro40 µg was superior to Engerix 20 µg (64% vs 27%) in a small study of HIV+ subjects non-responders to HBV vaccine (3), and BHIVA guidelines now recommend high dose HBV vaccine (40 µg) in all HIV-infected individuals***

- 4) BMI was the only significant predictor of anti-HBs response at week 28, while age, CD4 cell count, smoking status and HIV viral load were not significantly associated with the response.
- 5) systemic safety was good, without difference between groups, with 10 vaccine discontinuations, only one of them being related to a SAE. A higher rate of local adverse events was observed with double dose vaccination (15% vs 4%), as in the HB03 trial (42% vs 27%).
- 6) no significant variation was observed in the CD4 cell count between day 0 and week 28 (mean difference 15.2, P=0.800 for comparison between day 0 and week 28) and in HIV viral load (data not shown).

➔ **In HIV+ patients, non-responders to previous HBV vaccine, we recommend 3 doses of 40 µg HBV vaccine, as it is superior to 3 doses of 20 µg at W72 (49% vs 29% with anti-HBs > 10 mIU/mL, with higher anti-HBs titers at W28 + 72)**