Vaccination with Fendrix of prior nonresponding patients with HIV has a high success rate

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Background: Patients with HIV have a poor serological conversion rate with the standard vaccination strategy against hepatitis B virus (HBV) of around 50%. Vaccination with Fendrix confers much better results in these patients. In this study, we tested the effect of revaccination with Fendrix in prior nonresponding patients with HIV and aimed to determine which factors are associated with seroconversion.

Methods: Eight Dutch HIV treatment centers participated in this retrospective study. Patients infected with HIV-1 and nonresponding to prior course of vaccination against HBV (anti-HBs <10 IU/ml) and who had Fendrix as a second, third or fourth effort to achieve seroconversion were eligible for inclusion. Primary outcome was the proportion of patients with seroconversion after revaccination with Fendrix. Univariate binary logistic regression analyses were used to determine which factors could be used as predictors for seroconversions.

Results: We included 100 patients with HIV. The mean age was 47.3 (±11.0) years and 86% were men. Revaccination with Fendrix showed a seroconversion rate of 81% (95% confidence interval 72–88%). Median nadir $CD4^+$ cell count was 300 (20–1040) cells/μl and median $CD4^+$ cell count at the time at starting vaccination with Fendrix was 605 (210–1190) cells/μl. Regression analyses showed no significant factor associated with seroconversion.

Conclusions: Revaccination with Fendrix of patients prior nonresponding to other hepatitis B vaccination strategies has a high success rate. Eighty-one percentage responded with seroconversion, irrespective of $CD4^+$ cell count.

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Introduction

Worldwide, an estimated 10% of the 34 million patients with HIV have chronic hepatitis B virus (HBV) co-infection [1]. In countries with a low prevalence of chronic HBV infection, the high rate of co-infection with HBV is due to the shared transmission route including sexual contact and intravenous drug use. Patients with HIV harbor an increased risk of hepatitis B becoming chronic. The prevalence of chronic HBV infection in the Netherlands in 2013 was 6.8 per 100 000 [2]. HBV co-infection was reported in 7% of the Dutch patients with HIV in 2017 [3]. Individuals with chronic HBV infection have an increased risk of developing cirrhosis, liver failure or hepatocellular carcinoma [4–6].

The Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents released by the National Institutes of Health, the Centers for Disease Control and Prevention and the HIV Medicine Association of the Infectious Diseases Society of America recommend that all patients with HIV and without chronic HBV or immunity to HBV should be vaccinated against HBV [7]. Hepatitis B vaccine intramuscular or combined hepatitis A virus (HAV) and hepatitis B vaccine (Twinrix) as a three or four-dose series are recommended for protection against HBV [7]. In the Netherlands, hepatitis B vaccination is available free of charge for risk groups (e.g. sex workers, injecting drug users and MSM).

A review of the immunological response after hepatitis B vaccination in adults with HIV reported a wide diversity of seroconversion after the standard schedule of vaccination, ranging from 34 to 88.6% [8]. A study performed by Launay *et al.* [14] reported a seroconversion rate of 82% when vaccinated with four double doses intramuscular. A previous study in the Netherlands has shown that only 50% of patients with HIV have an antibody response to the initial hepatitis B vaccination consisting of three doses of 10 μg of HBvaxPro, given when the $CD4^+$ cell count is above 350 cells/μl [9]. Lower nadir $CD4^+$ cell count, older age, uncontrolled HIV replication and obesity (BMI $>30\,kg/m^2$) are factors associated with a worse response to HBV vaccination [10–12].

To increase the response to hepatitis B revaccination in nonresponding patients with HIV, it is best to postpone the revaccination until the viral load is undetectable as a result of the use of antiretroviral therapy (ART) or the $CD4^+$ cell count is above 350 cells/μl [13]. There are several revaccination strategies, including giving a double dose vaccine at 0, 1 and 2-month schedule, or a 0, 1 and 6-month schedule [7,13,14]. Another strategy is to revaccinate with Twinrix [7]. Between 4 and 6 weeks after completion of the vaccine series, it is advised to measure anti-HBs titer due to diminished response.

Fendrix contains 20 μg recombinant HB surface antigen, and in contrast to other HBV vaccines, the adjuvant AS04 – a Toll-like receptor 4 (TLR4) agonist and aluminium phosphate. TLR4 agonists promote cytokine release and increase the number of activated antigen presenting cells, leading to a larger antigen-specific T-cell activation [16]. Since 2005, it has been licensed in Europe for patients with renal insufficiency older than 15 years, but it is not licensed for patients with HIV. A previous study has shown that revaccination with Fendrix in immunocompetent persons performed significantly better compared to the revaccination scheme using three Engerix-B doses [15]. To our knowledge, only one study exists that studied the effect of Fendrix as a revaccination strategy in patients with HIV. However, this is a small study that included only 22 patients who showed a seroconversion rate of 81.8% [16]. The aim of this study was to describe the experience with revaccination with Fendrix in patients with HIV in Dutch HIV treatment centers and to determine which factors are associated with seroconversion after revaccination.

Methods

We conducted a retrospective multicenter study. All the Dutch HIV treatment centers, including university medical centers and large regional hospitals that had used Fendrix as a revaccination strategy, were asked to participate. Patients infected with HIV-1 and nonresponding to prior vaccination against HBV (defined as anti-HBs <10 IU/ml), and who had Fendrix as a second, third of fourth effort to achieve adequate anti-HBV titers were eligible for inclusion.

Two of the participating centers were visited by one of the investigators (E.E.B. or Pv.B.) to obtain the required data by using electronic patient files. In the other centers, the data were collected by one of the treating physicians and forwarded anonymously by e-mail.

Sex, country of birth, nadir $CD4^+$ cell count (defined as the lowest $CD4^+$ cell count measured at any point in time, but before start of vaccination with Fendrix), the date started with ART, the type of vaccine given, the vaccination scheme, the dosage and whether a patient showed seroconversion after revaccination were recorded. Age, length, weight, BMI, $CD4^+$ cell count and viral load, seroconversion after revaccination with Fendrix, type of ART (e.g. protease inhibitor-based, non-nucleoside reverse transcriptase inhibitor-based, integrase inhibitor based) and the revaccination scheme (e.g. 0, 1, 2, 6 months) were also recorded.

Univariate binary logistic regression was used to determine which factors could be used as predictors for a successful seroconversion (anti-HBs ≥10 IU/ml)

after revaccination. For the statistical analyses, we used SPSS, version 23 (IBM Corp., Armonk, NY, USA). All data are reported as mean ± standard deviation, or as median and range. Missing data were treated as missing. Confidence intervals (CI) for proportions were calculated using the exact Clopper–Pearson method.

The Medical Ethics Committee of the University Medical Center Groningen (UMCG) concluded that this study was in accordance with Dutch Law (METc 2015/367) and does not meet the criteria of the Medical Research Involving Human Subjects Act (WMO).

Results

Eight HIV treatment centers agreed to participate and had used Fendrix as a revaccination strategy. Of these eight hospitals, five were university medical centers and three were large regional hospitals. We received data of 100 patients with HIV who were all revaccinated with Fendrix and these patients were included. They were nonresponders to previous HBV vaccination schedules. The included patients had a mean age of 47.3 (±11) years. The majority of the patients were men (86%) (Table 1).

Of the 100 included patients, 81% (95% CI 72–88%) of the prior nonresponders revaccinated with Fendrix had a successful serological response (Table 1). Male patients responded in 81.4% with seroconversion, female patients responded in 78.6% with seroconversion ($P = 0.803$). The median nadir $CD4^+$ cell count in the patients not responding to Fendrix was 300 cells/μl. The median nadir $CD4^+$ cell count in the patients responding to Fendrix was 303 cells/μl ($P = 0.371$). The $CD4^+$ cell count at the time of starting with Fendrix vaccination was 785 (210–1080) cells/μl in the nonresponding group and 595 (240–1190) cells/μl in the responding group ($P = 0.170$).

Univariate binary logistic regression analyses showed no significant difference in nadir $CD4^+$ cell count, age, sex, BMI, viral load or the cumulative vaccination dosage (Table 2). There appeared to be a trend towards a significant association between $CD4^+$ cell count and $CD8^+$ cell count and response to Fendrix.

Table 1. Baseline characteristics ($N = 100$).

Variable	Result
Male sex ($n = 100$), *n* (%)	86 (86)
Age ($n = 100$) (years, mean)	47.3 ± 10.9
Dutch nationality ($n = 99$), n (%)	79 (79.8)
Median BMI ($n = 100$, kg/m^2) (range)	25.7 (15.1 to 45.6)
Median years on treatment before starting with Fendrix ($n = 87$), (range)	2.0 (−2 to 17)
Median $CD4^+$ nadir before vaccination with Fendrix ($n = 99$, cells/μl) (range)	300 (20 to 1040)
Viral load at time of Fendrix of <50 copies/ml ($n = 95$), *n* (%)	79 (83.2)
Median $CD4^+$ at time of vaccination with Fendrix ($n = 96$, cells/μl) (range)	605 (210 to 1190)
Median $CD8^+$ at time of vaccination with Fendrix ($n = 76$, cells/μl) (range)	810 (0 to 2645)
Patients with $CD4^+$ <350 cells/μl at time of vaccination with Fendrix ($n = 100$), *n* (%)	4 (4)
Patients with $CD4^+$ ≥350 cells/μl at time of vaccination with Fendrix ($n = 100$), *n* (%)	96 (96)
Type of vaccine used for first vaccine series ($n = 80$)	
First vaccine series with Engerix, *n* (%)	31 (38.8)
First vaccine series with Twinrix, *n* (%)	15 (18.8)
First vaccine series with HbVaxPro, *n* (%)	32 (40.0)
First vaccine series with other, *n* (%)	2 (2.6)
Type of ART used ($n = 97$)	
ART PI-based, n (%)	12 (12.4)
ART NNRTI/NRTI, n (%)	52 (53.6)
ART PI-based+ NNRTI/NRTI, *n* (%)	19 (19.6)
ART other, *n* (%)	6 (6.2)
No ART, *n* (%)	8 (8.2)
Number of previous vaccines series before Fendrix ($n = 89$)	89
Fendrix as second vaccine after prior vaccination, *n* (%)	25 (28.1)
Fendrix as third vaccine after prior vaccination, *n* (%)	53 (59.6)
Fendrix as >third vaccine after prior vaccination, *n* (%)	11 (12.4)
Vaccination scheme used for Fendrix ($n = 87$)	87
Fendrix scheme 0 month, *n* (%)	14 (16.1)
Fendrix scheme 0–1–6 month, *n* (%)	26 (29.9)
Fendrix scheme 0–1–2–6 month, *n* (%)	41 (47.1)
Fendrix scheme other, *n* (%)	6 (6.9)
Response to Fendrix ($n = 100$, anti-HBs >10 IU/ml), *n* (%)	81 (81)

Data are reported as mean ± SD or as median with range. ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation.

Table 2. Predictors of response to Fendrix ($N = 100$).

Independent variable	Response to Fendrix ($n = 81$)	No response to Fendrix ($n = 19$)	Univariate analysis, P value
Age (years, mean)	47.5 ± 11.6	46.7 ± 8.0	0.772
Sex (male, %)	86.4	84.2	0.803
BMI (kg/m^2, median)	26.0 (15.0–45.6)	24.2 (17.8–34.8)	0.554
Nadir CD4$^+$ (cells/μl, median)[a]	303.0 (20–900)	300.0 (20–1040)	0.626
Median CD4$^+$ at start Fendrix (cells/μl) (range)	595.0 (240–1190)	785.0 (210–1080)	0.079
Median CD8$^+$ at start Fendrix (cells/μl) (range)	1160.0 (0–2110)	780.0 (130–2645)	0.083
Median CD4$^+$/CD8$^+$ ratio (range)	0.72 (0.18–4.38)	0.66 (0.14–3.89)	0.529
Viral load <50 copies/ml at start Fendrix (%)	83.1	83.3	0.982
Number of previous vaccination schemes[b]	$n = 73$	$n = 16$	
Second series, n (%)	20 (27.4)	5 (31.3)	0.630
Third series, n (%)	45 (61.6)	8 (50.0)	0.337
>Third series, n (%)	8 (11.0)	3 (18.8)	0.609
Fendrix vaccination scheme[c]	$n = 72$	$n = 15$	
Scheme 0 month (n, %)	11 (15.3)	3 (20.0)	0.576
Scheme 0–1–6 month (n, %)	23 (31.9)	3 (20.0)	0.206
Scheme 0–1–2–6 month (n, %)	34 (47.2)	7 (46.7)	0.356
Other (n, %)	6 (6.9)	4 (13.3)	0.625

Data are reported as mean ± SD or as median with range. ART, antiretroviral therapy; SD, standard deviation.
[a]Only patients where the date of nadir CD4$^+$ lies before start of Fendrix.
[b]Number of previous vaccinations was missing for eight patients in the responding group and in three patients in the nonresponding group.
[c]Vaccination schema was missing for seven patients in the responding group and two patients in the nonresponding group.

Discussion

In this retrospective analysis of 100 patients with HIV and nonresponding to prior hepatitis B vaccination, Fendrix showed a high seroconversion rate of 81%, irrespective of the Fendrix scheme used or the amount of vaccines given. This is a remarkably high seroconversion rate in these patients, as many of the patients had failed not only once, but also a second or third hepatitis B vaccination series before the Fendrix vaccination scheme. This result confirms the seroconversion rate previously found in a small study on the immunogenicity of Fendrix in 22 nonresponding adults with HIV, conducted by De Silva *et al.* [16], which found a similar success rate of 81.8%. We included 100 patients, making this study much larger. These rates are higher than previously conducted studies that tested other revaccination regimes. Rey *et al.* [17] reported seroconversion rates in nonresponding patients with HIV after they were revaccinated either with 20 or 40 μg recombinant hepatitis B vaccine of 67 and 74%. Pettit *et al.* [11] found a similar seroconversion rate of 66.7% after revaccination with 40 μg Engerix-B.

In contrast with some previous studies, in which a lower nadir CD4$^+$ cell count, a lower CD4$^+$ cell count at the time of vaccination or a lower CD4$^+$/CD8$^+$ cell ratio was associated with a lower seroconversion rate [10,18,19], we found no association between any of these parameters and response to vaccination with Fendrix. This could be explained by the relatively good immune status of our cohort. In fact, in only four patients of our cohort, the CD4$^+$ cell count was below 350 cells/μl at the time of vaccination (two in each group), thus precluding an assessment of the effect of a low CD4$^+$ cell count on vaccination response. Unexpectedly, there appeared to be a trend towards a higher CD4$^+$ cell count an lower CD8$^+$ cell count in the nonresponding group, and *vice versa* but, because almost none of the patients had a low CD4$^+$ cell count, we doubt the clinical relevance of this finding. Moreover, in our study, CD4$^+$/CD8$^+$ cell ratio was not significantly different between the responding and nonresponding group.

We found no significant association between weight, age or viral load, in contrast to previous studies in this patient population [9,10] Furthermore, cumulative doses of Fendrix were not associated with a higher chance of seroconversion. Based on these findings, it seems that the increased rate of seroconversion with Fendrix might be attributable to the composition and immunogenicity of Fendrix.

The main strength of this study is that we were able to assess the seroconversion rate after Fendrix vaccination in the largest group of nonresponding patients with HIV thus far. This also allowed us to study the effect of the number and type of vaccinations used before Fendrix on seroconversion rate. As a result, we found that the number of dosages before Fendrix were not associated with higher chance of seroconversion.

The study has several limitations, including its retrospective nature. There was no standard protocol for revaccination with Fendrix, patients had used a variety of types of revaccinations strategies with Fendrix, for example, single and double dosages and different revaccination schemes. However, we found no significant association between the revaccination strategy and response to Fendrix vaccination. We also did not record the exact titer of anti-HBs after revaccination with

Fendrix, only whether the titer of anti-HBs was above or below 10 IU/ml.

In conclusion, vaccination with Fendrix has a high success rate of 81% irrespective of nadir $CD4^+$ cell count or $CD4^+$ cell count at the time of revaccination. Based on this high success rate, we recommend a prospective trial, in which patients with HIV are vaccinated with Fendrix as first-line hepatitis B vaccination or to the current standard hepatitis B vaccination, including a cost-effectiveness analysis. In the meantime, we advise considering the use of Fendrix as a revaccination strategy after failure of the first-line vaccination strategy.

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Conflicts of interest

GlaxoSmithKline provided Fendrix to Td.V. free of charge. For the remaining authors, none were declared.

Fendrix has not yet been approved by the US FDA or the EMA for vaccination of patients with HIV.

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