Comparative efficacy of an intensified re-vaccination scheme for Hepatitis B virus infection among patients infected with HIV (CORE-HIV): A Randomized Controlled Trial. Study protocol

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Study Title:

Comparative Efficacy of an Intensified Re-vaccination Scheme for Hepatitis B Virus Infection Among Patients Infected With HIV: A Randomised Trial (CORE-HIV)

Study Rationale:

Vaccination against hepatitis B is commonly prescribed among patients living with HIV. However, current research has shown a lower response to this vaccine, which often ranges between 34% to 65%. Several guidelines have recommended revaccination for non-responders, but many uncertainties remain regarding specific schedules and dosing schemes. This situation is partially explained in the lack of randomised trials comparing different vaccination strategies. The purpose of this study is to determine the effectiveness of an intensified immunisation schedule as contrasted to a standard-dose one in increasing the serological response to the hepatitis B virus. Revaccination is recommended at monthly intervals.
Arm 1: standard-dose vaccine at 0, 4 and 8 weeks.
Arm 2: double-dose vaccine at 0, 4 and 8 weeks.

Hypothesis

¿Among patients living with HIV and with a failed serological response to a standard hepatitis-B virus vaccine, does the use of an intensified strategy (40mcg) as compared to a standard revaccination (20mcg) increase serological response rates?

H0: Nonresponding patients living with HIV will not have a different response rate to an intensified scheme of the hepatitis B virus vaccine as compared to a standard strategy.

H1: Nonresponding patients living with HIV will have a different response rate to an intensified scheme of the hepatitis B virus vaccine as compared to a standard strategy.

Primary Objective(s) / Endpoint(s)

Serologic Response, defined as presence of anti-HBs greater than 10 ui/ml, 4-8 weeks after completion of the allocated vaccination scheme.

Secondary Objective(s) / Endpoint(s)

- Serological response of anti-HBs >100 UI/L.
- Serological response at 1 year follow up
- Determine the frequency of local adverse reactions to the vaccine up to one week after exposure.
- Development of any systemic adverse reaction attributable to vaccination.

Treatment

Arms 1: experimental. Patients allocated to this arm will receive three doses of 40 mcg each of recombinant hepatitis B vaccine (Engerix-B ®). Doses will be administered at 0, 1 and 2 months.
Arm 2: Active comparator. Patients allocated to this arm will receive three doses of 20 mcg each of recombinant hepatitis B vaccine (Engerix-B ®). Doses will be administered at 0, 1 and 2 months.

Trial Population

Patients with HIV who fail to respond to a primary hepatitis B series vaccine from the outpatient clinic of the Infectology Unit of Hospital Gustavo Fricke, Viña del Mar, Chile. Older than 18 years of age, both genders.

Sample Size and Sample Size Justification

Sample size calculations were made considering an estimated difference of 25% in the primary outcome (serologic response to HBV vaccination 4 weeks after completion of the schedule) between the two groups, to achieve a power of 80% at a two-sided 0.05 significance level. As such, a sample size of 116 patients (58 per arm) was calculated.

Key Inclusion Criteria

Older than 18 years of age.
Patients infected with Human Immunodeficiency Virus (HIV)
Failed previous vaccination with a standard dose scheme of recombinant hepatitis B vaccine (20mcg at 0, 1 and 6 months). Nonresponders will be considered as those

patients presenting a hepatitis B surface antigen antibody titer lower than 10UI/mL 4 to 8 weeks after the last dose of the vaccine.
Provision of informed consent.

Key Exclusion Criteria

Proven Hepatitis B virus infection (acute or chronic).
Proven hypersensitivity to the vaccine or any of its components.
Current diagnosis of a solid organ neoplasia, decompensated chronic liver disease, chronic kidney disease, pregnancy or unexplained fever in the last 7 days were excluded from the trial. Patients undergoing treatment with systemic corticosteroids or other immunosuppresive medications were excluded as well.

Study Assessments

- Primary Outcome Measure: Serologic Response, 4 to 8 weeks after completion of the vaccination schemes.
- Secondary Outcome:
- Anti-HBs titres >100 UI/L.
- Serological response at 1 year follow up
- Safety Measures: local and systemic adverse reactions after each dose of vaccine.

Data and Statistical Plan

First, descriptive statistics will be performed to assess the characteristics of the study sample. The Fisher’s exact test will be used to evaluate the bivariate association of categorical variables. Quantitative variables will be compared using Mann–Whitney's or Student’s t-tests according to data distribution characteristics and variances, which will be assessed using histograms.

Analyses aimed to determine factors associated with a positive serological response will be performed using multivariate logistic regression techniques. Lineality of included variables will be assessed graphycally, and every included model will evaluate the existence of potential interactions during development. The final model's diagnostic accuracy will be established using ROC curves. Goodness of fit will be assessed using Hosmer's an Lemeshow's test.

This analysis plan will be performed by a statistician who will be unaware of both treatment allocation and clinical assessment of included patients using Stata v10.0® (StataCorp, 1996–2011).

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