SARS-CoV-2 vaccination response in people living with HIV

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Main study: primary vaccination regimenPrimary Objective: 1. To determine the difference in the antibody response against SARS-CoV-2 in PLWH 4 weeks after the completed vaccination schedule with one of the two available mRNA vaccines (BNT162b2 or...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Immunodeficiency syndromes
Study type	Observational invasive

Summary

ID

NL-OMON52193

Source
ToetsingOnline

Brief title
COVIH

Condition

- Immunodeficiency syndromes
- Viral infectious disorders

Synonym
coronavirus, SARS-CoV-2 virus

Research involving
Human

Sponsors and support

Primary sponsor: OLVG
Source(s) of monetary or material Support: ZonMW subsidie project number 10430072010008,AIDSfonds: small grant bij (kleine) ongedekte posten

Intervention

Keyword: people living with hiv, SARS-CoV2, vaccination

Outcome measures

Primary outcome

Main study: primary vaccination regimen

Primary Outcome:

1. Antibody response against SARS-CoV-2 in PLWH 4 weeks after the completed vaccination schedule with one of the two available mRNA vaccines (BNT162b2 or mRNA-1273) compared to non-HIV healthy controls.

Secondary outcome

Secondary Outcomes:

1. HIV-related (e.g. actual and nadir CD4 counts, plasma HIV-RNA) and HIV-unrelated variables (age, sex) that are associated with antibody response 4 weeks after the completed vaccination schedule with one of the two mRNA vaccines (BNT162b2 or mRNA-1273) in PLWH.

2. Antibody response in PLWH 4 weeks after the completed vaccination schedule with one of the two vector vaccines (AZD1222 and Ad26.COV2.S) compared to healthy controls.

3. HIV-related and HIV-unrelated factors that are associated with a week 4 post-vaccination response (Trimeric Spike IgG >=300 BAU/mL as well as non-response (IgG <50 BAU/ml).

4. To measure the Trimeric Spike IgG antibody titer (in BAU/mL) and N-specific antibodies at 6, 12, 18 and 24 months after the completed primary vaccination regimen in all participating PLWH from the 3 key centers (OLVG, Erasmus MC,

LUMC), in relation to clinical probability of intercurrent SARS-CoV-2 infection, and compared to HIV-negative controls.

5. To evaluate which HIV-related (e.g. actual and nadir CD4+ T-cell counts, plasma HIV-RNA) and HIV-unrelated variables (age, sex, primary vaccine type, timing and type of booster vaccinations, breakthrough infections) are associated with waning of SARS-CoV-2-specific antibodies over time, measured at week4, 6, 12, 18 and 24 months after completing the primary vaccination schedule.

6. Collecting data on breakthrough infections based on positive PCR, self-reported positive lateral flow test, or detection of N-specific antibodies at month 1, 6, 12, 18, and 24.

6. To describe adverse events in the 7 seven days after the primary vaccination(s), compared to healthy controls.

Substudy: additional Moderna vaccination in PLWH with hyporesponse

Primary Outcome:

1. To determine the mean increase in SARS-CoV-2 antibody response 28 days after the additional Moderna vaccination and the proportion of PLWH with an adequate serological response.

Secondary Outcomes:

1. To assess HIV-related (e.g. actual and nadir CD4+ T-cell counts, plasma HIV-RNA) and HIV-unrelated variables (age, sex, primary vaccine type) that are associated with the mean increase in antibody response 28 days after the additional Moderna vaccination.

2. To measure SARS-CoV-2-specific neutralizing antibodies and SARS-CoV-2-specific B/T-cell responses, all against relevant variants and according to primary vaccine type.
3. To assess the correlation between the SARS-CoV-2 antibodies and the SARS-CoV-2-specific neutralizing antibodies, and the correlation between the SARS-CoV-2 antibodies and the B/T-cell responses.
4. To describe adverse events in the 7 seven days after the additional Moderna vaccination.

Substudy: after each additional booster vaccination
Primary Outcome:
1. To evaluate the level and fold change in SARS-CoV-2 antibodies between day of boost and 28 days after each booster vaccination in PLWH compared to HIV-negative controls, according to primary responding and non-responding PLWH (<33.8 vs. >=33.8 BAU/mL after the primary vaccination regimen) and primary vaccine type (vector vs. mRNA).

1. To assess HIV-related (e.g. actual and nadir CD4+ T-cell counts, plasma HIV-RNA) and HIV-unrelated variables (age, sex, primary vaccine type) that are associated with the mean increase in antibody response in the 28 days after each booster vaccination.
2. To measure SARS-CoV-2-specific neutralizing antibodies and SARS-CoV-2-specific B/T-cell responses at day 0,7, 28, 90 and 180 in PLWH, all against relevant variants and according to primary vaccine type, and in

comparison to HIV-negative controls.

3. To assess HIV-related (e.g. actual and nadir CD4+ T-cell counts, plasma HIV-RNA) and HIV-unrelated variables (age, sex, primary vaccine type, timing and type of booster vaccinations, breakthrough infections) that are associated with the magnitude of the SARS-CoV-2-specific neutralizing antibodies and B/T-cell responses.

4. To assess the correlation between the SARS-CoV-2 antibodies and the SARS-CoV-2-specific neutralizing antibodies, and the correlation between the SARS-CoV-2 antibodies and the B/T-cell responses, both comparing these correlations to the ones found in HIV-negative controls.

5. To compare the SARS-CoV-2-specific antibodies between day 7 post boost and day 28 post boost and vice versa for the neutralizing antibodies, and B/T-cell responses.

6. To evaluate the waning of SARS-CoV-2 immune responses at day 90 and 180 compared to day 28 after the booster vaccination, compared to the waning in the HIV-negative controls.

7. Collecting data on breakthrough infections based on positive PCR, self-reported positive lateral flow test, or detection of N-specific antibodies at day 0, 28, 90 and 180 post boost.

8. Adverse events in the first seven days after each additional booster vaccination in PWH, compared to HIV-negative controls.

Exploratory Objective:

1. Evaluate the effect of vaccinations on the size and reactivation potential

of the HIV reservoir.

Study description

Background summary

SARS-CoV2 vaccines will be rapidly deployed in the Netherlands through a national vaccination programme from the beginning of 2021, following accelerated authorisation procedures. The Health Council has already advised that priority for vaccination will be given to older and vulnerable persons, and also to people with vital occupations, such as health workers.
People living with HIV (PLWHIV) are considered a vulnerable group because they are also designated for pneumococcal vaccination and the annual flu shot. There is evidence that PLWHIV with lowered immunity have an increased risk of a more severe COVID19 course. SARS-CoV2 vaccination could well prevent this.
It is known that PLWHIV can have reduced effectiveness on regular vaccinations. In the upcoming SARSCoV2 studies, PLWHIV were included in some phase 3 studies, but specific data on efficacy in this group has
not yet made public. It is clear, however, that the numbers of PLWHIV in those initial studies were small and will therefore provide little differentiated information on response in this group. Certainly in the case of PLWHIV with low immunity, a lower response rate can be expected. It is therefore important to obtain better information in this group.
In the Netherlands, several types of SARS-CoV2 vaccines will be in use in 2021: the mRNA vaccines of BioNTech&Pfizer and Moderna, as well as the vaccine based on a modified replication-deficient adenovirus of the University of Oxford & AstraZeneca and the vaccine of Janssen &Johnson. In all of these vaccines, phase 3 trials correlated clinical effectiveness with the presence of neutralising antibodies against the receptor-binding part of the SARS-CoV2, which was induced by the vaccination.
In the current study, therefore, vaccine effectiveness in PLWHIV will be assessed by measuring the presence of sufficient of these antibodies after vaccination.
For participants with an insufficient response after standard vaccination, a one-time booster with Moderna will be offered, after which the immunity against SARS-CoV2 will be studied again.
In addition, in participants from the 3 key centres (OLVG, Erasmus MC, LUMC), the immunity against SARS-CoV-2 will be followed up half yearly.

Furthermore, volunteering participants will donate blood before and 7, 28, 90 and 180 days after each booster vaccination.

Study objective

Main study: primary vaccination regimen
Primary Objective:
1. To determine the difference in the antibody response against SARS-CoV-2 in PLWH 4 weeks after the completed vaccination schedule with one of the two available mRNA vaccines (BNT162b2 or mRNA-1273) compared to non-HIV healthy controls.

Secondary Objectives:
1. To assess HIV-related (e.g. actual and nadir CD4 counts, plasma HIVRNA) and HIV-unrelated variables (age, sex) that are associated with antibody response 4 weeks after the last vaccination with one of the two mRNA vaccines (BNT162b2 or mRNA-1273) in PLWH.
2. To determine the antibody response in PLWH 4 weeks after the completed vaccination schedule with one of the two vector vaccines (AZD1222 and Ad26.COV2.S) compared to healthy controls.
3. To evaluate which HIV-related and HIV-unrelated factors are associated with antibody response 4 weeks after the last vaccination with one of the two vector vaccines (AZD1222 and Ad26.COV2.S).
4. To determine the duration of serologic anti-SARS-CoV-2 immune responses over time in PLWH.
5. To evaluate which HIV-related and HIV-unrelated variables are associated with waning of serologic SARS-CoV-2 immune responses over time.
6. To examine the incidence of breakthrough infections in PLWH.
6. To determine the difference in reactogenicity after vaccination between PLWH.

Substudy: additional Moderna vaccination in PLWH with hyporesponse
Primary Objective:
1. To evaluate the SARS-CoV-2 antibody response after one additional Moderna vaccination in participants who have an insufficient antibody response after the primary vaccination regimen.

Secondary Objectives:
1. To assess HIV-related and HIV-unrelated variables that are associated with the mean increase in antibody response after the additional Moderna vaccination.
2. To evaluate the breadth of the immune responses after the additional Moderna vaccination.
3. To assess the predictive value of the antibody response on the in-depth immune responses.
4. To describe reactogenicity after the additional Moderna vaccination.

Substudy: after each additional booster vaccination
Primary Objective:
1. To determine the difference in SARS-CoV-2 antibody response after each booster vaccination in PLWH compared to HIV-negative controls.

Secondary Objectives:
1. To assess HIV-related and HIV-unrelated variables that are associated with

the antibody response after each booster vaccination in PLWH.
2. To evaluate the breadth of the immune responses after each booster vaccination in PLWH compared to HIV-negative controls.
3. To assess HIV-related and HIV-unrelated factors that are associated with the in-depth immune responses.
4. To assess the predictive value of the antibody response on the in-depth immune responses.
5. To assess the predictive value of immune responses on day 7 post boost.
6. To evaluate the waning of SARS-CoV-2 immune responses after each booster vaccination compared to HIV-negative controls.
7. To examine the incidence of breakthrough infections before and during study period in PLWH compared to HIV-negative controls.
8. To describe reactogenicity in the 7 seven days after each booster vaccination in PLWH.

Exploratory Objective:
1. Evaluate the effect of vaccinations on the size and reactivation potential of the HIV reservoir.

Study design

Observational study in a cohort of people living with HIV (PLWHIV). This group of patients visits the outpatient clinic at least every two years for their regular HIV check-up and more often in case of clinical or comorbidity events. The baseline characteristics are uniform and very well documented, as they all participate in a longitudinal, national database controlled by Stichting HIV Monitoring.
Participants will receive an invitation to be vaccinated against SARS-CoV-2, most likely through their GP, but possibly also through the GGD, according to national regulations. After this invitation, they will visit the Infectious Diseases Outpatient Clinic of their hospital to have blood sampled before receiving their SARS-CoV-2 vaccine and 4 weeks after the last vaccination. In total, they will visit the outpatient clinic up to two times extra for this study (three times extra for the substudy participants).
All serum samples collected for the primary endpoint will first be analysed for serological response. If a patient is found to be a non- or hyporesponder on the primary vaccination series, he will be invited for a booster (Moderna), which will be administered at LUMC or Erasmus MC. Observational study in a cohort of people living with HIV (PLWHIV). This group of patients visits the outpatient clinic at least every two years for their regular HIV check-up and more often in case of clinical or comorbidity events. The baseline characteristics are uniform and very well documented, as they all participate in a longitudinal, national database controlled by Stichting HIV Monitoring.
Participants will receive an invitation to be vaccinated against SARS-CoV-2, most likely through their GP, but possibly also through the GGD, according to national regulations. After this invitation, they will visit the Infectious Diseases Outpatient Clinic of

their hospital to have blood sampled before receiving their SARS-CoV-2 vaccine and 4 weeks after the last vaccination. In total, they will visit the outpatient clinic up to two times extra for this study (three times extra for the substudy participants). All serum samples collected for the primary endpoint will first be analysed for serological response. If a patient is found to be a non- or hyporesponder on the primary vaccination series, he will be invited for an additional vaccination (Moderna), which will be administered at the LUMC or Erasmus MC. The participants receiving the additional vaccination will be sampled shortly before the booster and 4 weeks afterwards. To evaluate the durability of the immune response after vaccination, and along with that the protection against infection, antibody concentrations will be measured in half yearly taken sera from the participants of the 3 key centres (OLVG, Erasmus MC, LUMC). Furthermore, participants can choose to donate blood before and 7, 28, 90, 180 days after each additional booster vaccination, to evaluate the effect of additional booster vaccinations in this group. The study will start as soon as PLWHIV vaccination starts and will recruit patients for an expected duration of 6 months or less if the sample size is reached.

For participants in the primary vaccination cycle, the duration per visit will be approximately 15 minutes. For the first 2 study visits, 10 ml of blood will be collected, up to 20 ml in total.
In the substudy, 40 mL of additional blood will be drawn per visit for PBMC collection, 80 mL in total in 2 months. Also in this subgroup, a third additional visit is planned 3 weeks after the 1st vaccination (10 mL serum).
The non- or hyporesponders who receive an additional Moderna vaccine will have 2 additional visits with 40 mL of blood collected at each visit (shortly before and 4 weeks after the booster).
The participants from the substudy will have 5 extra visits around each booster vaccination, with a maximum of 40mL blood taken per visit (day 0, 7, 28, 90, 180).
Patients from OLVG, LUMC, Erasmus MC will also be followed in routine care for 24 months after completion of the primary vaccination cycle. Additional SARS-CoV2 serology will then be determined from their blood samples taken for their regular HIV checks (every six months). In addition, participants will be asked to complete a standardised diary on vaccination-related side effects one week after each vaccination.

There will be a control group of non-HIV infected people who have received their vaccination for COVID-19. The control group will consist of both self-recruited healthy controls (control group A) and healthy controls that were already recruited in other COVID vaccination trials in the Netherlands and used the same methods to measure the antibody response (control group B). Participants in control group A will have at least one study visit approximately 1 month after vaccination and optionally at months 6, 12, 18 and 24 for a maximum of 4 additional visits. Since PBMC from 1 self-recruited healthy control can be used as a control for more than 1 PLWHIV in the

experiments, up to 100 mL can be collected at each visit. This will accumulate to a total of up to
500 mL over 2 years of follow-up. The control group will not be asked to fill in a diary regarding side effects after vaccination. Control group B consists of 2 populations. The first are health care workers from the Erasmus Medical Centre who participated in a COVID-19 vaccination trial. They were aged 18 years or older and employed at Erasmus MC and were recruited at the occupational health department for SARS-CoV-2 testing where they could participate in the study SARS-CoV-2 serology was determined approximately 28 days after the last vaccination. Data collected included gender, age and type of vaccine. The group consisted of people vaccinated with the Moderna and Pfizer mRNA vaccines and, to a lesser extent, people vaccinated with Janssen or AstraZeneca. The second part of control group B consists of data from healthy controls recruited in the VACOPID COVID-19 vaccination study. Inclusion criteria were age 18 years or older and no known immunodeficiency. The control group consisted of 200 family members or household members of the included participants, with an age range of 18 to 75 years and equal gender distribution, who were all vaccinated with Moderna.

Study burden and risks

The burden is limited, since the only additional burden for all participants is the venipuncture to obtain a serum sample (with the risk of blood loss) twice and the short questionnaires mentioned above are administered twice. Participants in the booster study will again have two venipunctures and a questionnaire administered.
Participants from the substudy will have 5 venipunctures around each additional booster vaccination, plus a questionnaire administered for each additional booster vaccine.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- 18 years or older
- Confirmed HIV infection
- Selected by national regulations for SARS-CoV2 vaccination
- Active participant in the follow-up of the Stichting HIV monitoring

Exclusion criteria

a history of a previous SARS-CoV2 infection (proven by PCR or positive serology). For participation in substudy previous SARS-CoV2 is no reason for exclusion

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-06-2021
Enrollment:	1650
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	COVID19 Comirnaty Original/Omicron BA.1
Product type:	Medicine
Brand name:	COVID19 Comirnaty Original/Omicron BA.4-5
Product type:	Medicine
Brand name:	COVID19 Spikevax Bivalent Original/Omicron BA.1
Product type:	Medicine
Brand name:	COVID19 vaccine Astra Zeneca (ChAdOx1-S recombinant)
Product type:	Medicine
Brand name:	COVID19 vaccine Janssen (Ad26.COV2-S)

Ethics review

Approved WMO Date:	20-01-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-02-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-02-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	08-03-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-07-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-12-2021

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-04-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-10-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-10-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-06-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-07-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 26993
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2021-001054-57-NL
CCMO	NL76562.100.21
Other	NL9214
OMON	NL-OMON26993