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CTN 328: Immunogenicity outcomes in people living with HIV in Canada following vaccination for COVID-19 (HIV-COV)-Protocol for an observational cohort study

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Keywords:	HIV & AIDS < INFECTIOUS DISEASES, COVID-19, IMMUNOLOGY, VIROLOGY

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Manuscripts

PROTOCOL

CTN 328: Immunogenicity outcomes in people living with HIV in Canada following vaccination for COVID-19 (HIV-COV)-Protocol for an observational cohort study

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ABSTRACT

Introduction: Most existing vaccines require higher or additional doses or adjuvants to provide similar protection for people living with HIV (PLWH) compared to HIV-uninfected individuals. Additional research is necessary to inform COVID-19 vaccine use in PLWH.

Methods and analysis: This multi-centred observational Canadian cohort study will enroll 400 PLWH aged ≥ 16 years from Montreal, Ottawa, Toronto and Vancouver. Subpopulations of PLWH of interest will include: 1) >55 years of age 2) CD4 counts <350 cells/mm³ 3) multimorbidity (≥ 2 comorbidities) and 4) “stable” or “reference” PLWH (CD4 T cells ≥ 350 cells/mm³, suppressed viral load for ≥ 6 months and ≤ 1 comorbidity). Data for 1000 HIV-negative controls will be obtained via a parallel cohort study (Stop the Spread Ottawa) using similar time points and methods. Participants receiving ≥ 1 COVID-19 vaccine will attend 5 visits: pre-vaccination; 1 month following the first vaccine dose; and at 3, 6 and 12 months following the second vaccine dose. The primary endpoint will be the percentage of PLWH with COVID-19-specific antibodies at 6 months following the second vaccine dose. Humoral and cell-mediated immune responses, and the interplay between T cell phenotypes and inflammatory markers, will be described. Regression techniques will be used to compare COVID-19-specific immune responses to determine whether there are differences between the “unstable” (CD4 <350) PLWH group, the stable PLWH cohort and the HIV-negative controls, controlling for factors that are believed to be associated with immune response. Unadjusted analyses will reveal whether there are differences driving factors associated with group membership.

Ethics and Dissemination: Written informed consent will be obtained from all study participants prior to enrolment. These findings will inform the design of future COVID-19 clinical trials, dosing strategies aimed to improve immune responses and guideline development for PLWH.

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3 **Trial registration:** [clinicaltrials.gov NCT04894448](https://clinicaltrials.gov/ct2/show/study/NCT04894448)
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6 **Keywords:** HIV; COVID-19; observational study; COVID-19 vaccines; vaccine immunogenicity
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14 **Strengths and Limitations of this study**
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- 16
17 • The largest and most comprehensive immunogenicity study in people living with HIV in
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19 Canada receiving COVID-19 vaccination
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22 • Emphasis on recruiting participants frequently excluded from pharmaceutical company-
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24 sponsored trials and those most likely to have poor outcomes following COVID-19
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26 infection (including individuals of older age, immune non-responders and persons with
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28 multimorbidity)
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32 • Assays used will enable differentiation between individuals with immunity from natural
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34 COVID-19 infection *vs.* vaccine-induced immunity, in addition to detection of immunity
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36 towards key variants of concern (VOCs)
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39 • Involvement of community members from study conception to protocol development and
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41 study implementation
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44 • Limitations include relatively late study start, recruitment restricted to major urban centres
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46 and variations in timing between vaccine doses amongst participants
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BACKGROUND

In Canada today, an estimated 67,000 people are living with HIV (PLWH), 30% of whom are immune non-responders,¹ defined as achieving undetectable HIV viral levels without robust CD4 T cell count recovery (<350 cells/mm³). Even with fully suppressed viral load on antiretroviral therapy (ART), chronic HIV infection is characterized by a low-grade elevation in pro-inflammatory and procoagulant biomarkers linked with higher mortality²⁻⁴. Poor immunogenicity to common vaccines, including influenza⁵, pneumococcal^{6,7}, meningococcal^{6,7} and hepatitis A⁸⁻¹⁰ and B vaccines,¹¹⁻¹³ is well-documented in PLWH with low CD4 T cell counts (<200 cells/mm³) and unsuppressed viral loads¹⁴⁻¹⁶. PLWH face other intersecting vulnerabilities that increase their risk of SARS-CoV-2 acquisition and symptomatic/severe COVID-19; they commonly belong to low socioeconomic or racialized groups disproportionately affected by COVID-19 and have higher rates of risk factors for severe COVID-19 disease (e.g., multiple chronic comorbidities).¹⁷⁻¹⁹ Yet, this priority population has been understudied in COVID-19 vaccine clinical trials.^{3, 20} Most HIV seropositive participants enrolled in COVID-19 vaccine trials had normal CD4 T cell counts (>500

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3 cells/mm³) and few comorbidities.^{21,22} As such, the immunogenicity results may not represent the
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6
7 wide spectrum of PLWH who are followed in Canadian centres today.
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14 For the AstraZeneca/Oxford COVID-19 vaccine trial (ChAdOx1, n=160 PLWH) inclusion criteria
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16 specified younger age (<55 years old) and high CD4 T cell count (>350 cells/mm³) while
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18 excluding medical comorbidities (e.g., heart, kidney, liver, respiratory diseases etc.).²¹ The data
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20 obtained from PLWH were not included in the primary publication.²¹ The Moderna trial included
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22 HIV-positive participants (n=176 PLWH) with CD4 T cell count ≥ 350 cells/mm³ and an
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24 undetectable HIV viral load within the past year.²³ COVID-19 infection developed in 11 PLWH
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26 who received placebo but none who received the Moderna vaccine. The Johnson and Johnson trial
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28 (n=1218 PLWH) included participants with “stable/well-controlled HIV infection” (defined as
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30 CD4 T cell counts ≥ 300 cells/ μ L within 6 months prior to screening and documented HIV viral
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32 load <50 copies/mL within 6 months prior to screening) but excluded participants with ongoing
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34 and progressive comorbidities associated with HIV infection.²⁴ COVID-19 infection developed in
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36 2 vaccinated PLWH and 4 PLWH given placebo. The Novavax trial, conducted in South Africa,
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38 excluded PLWH with chronic cardiovascular disease, gastrointestinal disease, liver disease, renal
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3 disease, endocrine disorder and neurological illness, as well as participants with very high body
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6 mass index (≥ 40 Kg/m²).²² As reported by Vivek *et al.*, efficacy of the NVX-CoV2373 Covid-19
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9 vaccine against the B.1.351 variant was examined in 1,857 individuals in South Africa, of whom
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13 30% (500 individuals) had HIV infection²⁵. The vaccine efficacy estimate in baseline seronegative
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16 HIV-negative participants was 52.2% (95% confidence interval: -24.8 to 81.7). During the first
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18
19 60 days of follow-up, the incidence of Covid-19 in HIV-negative placebo participants (5.3% [95%
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21
22 CI: 4.3 to 6.6) was comparable to the incidence in PLWH placebo participants with HIV (5.2%
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24 [95% CI: 3.6 to 7.2])²⁶. Among HIV-negative participants, there were four and two cases of
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27 symptomatic Covid-19 among NVX-CoV2373 and placebo recipients, respectively (N<109 in
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30 each group)²⁶. No cases were observed in the baseline HIV-positive population (N<33 in each
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33 group)²⁶. Among 94% of participants without HIV, vaccine efficacy was 60.1%. The study was
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36 not powered to detect efficacy in the small population of PLWH²⁶.
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41 In the ongoing CanSino study in Argentina, which includes approximately 900 PLWH,
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44 preliminary findings are not available to date. While several other trials included PLWH, they
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47 excluded their data from primary publication^{20,21,27}. In a recent report by Ruddy *et al.* which
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50 examined COVID-19 antibody response in 12 PLWH a median of 21 days (interquartile range 17-
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53 27) following the first dose of mRNA vaccine (50% Moderna and 50% Pfizer), antibodies were
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3 detected in all participants although lower levels were observed in persons with lower CD4 T cell
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6 counts²⁶. In this study, all 12 individuals were male, 8% were non-white, all had been on ART \geq 6
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9 months and 92% had an undetectable HIV viral load. Two individuals had a CD4 T cell count
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13 below 200 cell/mm³.²⁶
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17 We lack robust data on vaccine immunogenicity and immune response durability in
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20 subpopulations of PLWH. No evidence is available on the durability of immunogenicity in PLWH
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23 beyond 3 months following vaccination. Since the hallmark of HIV infection is a reduced number
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26 and function of CD4 T cells, and cell-mediated immunity has emerged as a critical aspect of the
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29 COVID-19 immune response,^{28,29,30} it is critical to characterize cellular immune and cytotoxic T
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32 cell responses to COVID-19 vaccination.³¹⁻³³
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35 Given that inflammatory markers may influence immune cell activation status and shift cell
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37 profiles towards either Th1 or Th2 responses, impacting vaccine-elicited immune response³⁴,
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39 understanding the interplay between immune activation and dysfunction is also important. To
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42 address this need, we are establishing a pan-Canadian prospective cohort of PLWH receiving
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45 COVID-19 vaccines to assess humoral and cellular immunogenicity and to describe the
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48 inflammatory milieu in this context. Safety and tolerability of COVID-19 vaccines in this cohort
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51 of PLWH will also be captured. Of note, COVID-19 vaccines currently approved for use in
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54 Canada include those manufactured by Pfizer, Moderna, AstraZeneca and Janssen (Johnston &
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3 Johnston) ([https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-](https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/list-drugs.html)
4 industry/drugs-vaccines-treatments/authorization/list-drugs.html). Since the beginning of the
5 vaccine roll-out Pfizer and Moderna vaccines were administered most often as they were the first
6 to gain approval by Health Canada. Furthermore, approved, due to concerns associated with
7 cerebral venous sinus thrombosis and vaccine-induced immune thrombotic thrombocytopenia, use
8 of the AstraZeneca COVID-19 vaccine has been restricted in some provinces. Furthermore, the
9 COVID-19 vaccine manufactured by Novavax is not licensed in Canada.
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23 **Study Objectives:**

24 Primary objective:

25 To evaluate the immunogenicity of COVID-19 vaccination in PLWH, as assessed by COVID-19-
26 specific immunoglobulin G antibody (IgG) enzyme-linked immunosorbent assay (ELISA), at 6
27 months following 2nd vaccine dose.
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35 Secondary objectives:

- 36 1) To assess neutralization capacity of COVID-19-specific IgG at 6 months following 2nd vaccine
37 dose.
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- 39 2) To assess the durability of COVID-19-specific IgG response in PLWH at 12 months following
40 vaccination.
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- 43 3) To examine changes in the proportion and activation phenotype of CD4 T cells, CD8 T cells, B
44 cells, natural killer cells and monocytes, including gene expression and cytokine production, pre-
45 and post-COVID-19 vaccination at 6 months following 2nd vaccine dose.
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3 4) To determine safety and tolerability of COVID-19 vaccines in PLWH, based on local or
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5 systemic adverse events following first or second injections.
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8 Exploratory objectives:
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11 1) To determine if subpopulations of PLWH respond differently to COVID-19 vaccination.
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13 Subpopulations of interest include, 1) PLWH >55 years of age; 2) immune non-responders (ART
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15 treated, and fully suppressed HIV RNA (<40 copies/mL), but CD4 T cell counts below 350
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17 cells/mm³ and CD4/CD8 T cell ratio <0.75); 3) PLWH with multimorbidity (2 or more chronic
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19 diseases) and 4) PLWH “reference” participants (with CD4 T cells >350 cells/mm³, suppressed
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21 viral load for at least 6 months, and have at most 1 comorbidity) (*Note: groups will not be mutually*
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23 *exclusive but will likely have overlapping characteristics*)
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28 (2) To investigate if current COVID-19 vaccines elicit IgG that cross-recognize key COVID-19
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30 variants of concern (VoC), and if this differs in PLWH compared to individuals without HIV
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33 (3) To compare virus-specific T cell responses generated by COVID-19 vaccines in PLWH and
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35 compare results with HIV-negative populations
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41 **METHODS AND ANALYSIS**

42 **Study design**

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46 This study is a multi-centre prospective observational cohort study. Approximately four hundred
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48 (400) PLWH aged ≥ 16 years will be recruited from 4 sites in 3 Canadian provinces including 1)
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50 McGill University Health Centre/Jewish General Hospital (Montreal), 2) Ottawa Hospital
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52 Research Institute, 3) The University Health Network (Toronto), and 4) St. Paul’s Hospital
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54 (Vancouver). Many sites provide HIV care for many clients who are visible minorities and
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3 multiple morbidities. This will enable our sites to recruit a study population representative of
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5 PLWH most likely to be impacted by detrimental COVID-19-related outcomes.¹⁹ Data for HIV-
6
7 negative individuals will be obtained from the Stop the Spread Ottawa (SSO) cohort. Since we
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9 will not perform additional analyses on the samples of the SSO cohort who we are going to include
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11 in our study, then we can include all the participants in the SSO study and matching of HIV-
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13 negative and HIV-positive participants will not be required.
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20 Determination of which vaccine is administered at which time point and to which individuals is
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22 dictated by Canada's provincial governments, with input from the National Advisory Committee
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24 on Immunization (NACI), and is not influenced by study investigators or staff. We will include
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26 participants irrespective of the specific type of COVID-19 vaccine. Furthermore, the duration of
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28 the interval between 1st and 2nd doses time from when the vaccine was administered will not
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30 influence eligibility, since Canada has decided to extend dose intervals for all 2 dose vaccines to
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32 4 months. However, the duration of interval between vaccine doses will included as an outcome
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34 variable.
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44 **Methods: Participants, intervention and comparator and outcomes**

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46 **Inclusion Criteria:** 1) Age ≥ 16 years; 2) HIV-positive for HIV group, immunocompetent and
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48 generally in good health for the HIV-negative group; and 3) Receiving ≥ 1 dose of COVID-19
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50 vaccine. Persons are still eligible to participate if they have already received one or two vaccine
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52 doses.
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3 **Exclusion Criteria:** 1) Receipt of any blood product or immunoglobulin preparation within 1
4 month of vaccine administration and until study completion; 2) signs/symptoms of active COVID-
5 19 at time of enrollment; 3) for the HIV-negative group: immune-compromising conditions or on
6 immunosuppressant medications. Prior receipt of other vaccines ≤ 12 months or past COVID-19
7 infection are not exclusion criteria but will be recorded. Detectable HIV viral load on ART is not
8 exclusionary.
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12 The following groups of PLWH will be prioritized for study enrolment:
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17 1. Older age (55 years and over). Older age is associated with immunosenescence and
18 results in lower vaccine efficacy.³⁵⁻³⁷ We have selected 55 as the specific age cut-off
19 since PLWH tend to develop comorbidities at an earlier age.
20
- 21
22 2. Immune non-responders (CD4 T cell count < 350 cells/mm³, CD4/CD8 < 0.75 with
23 undetectable viral load for 1+ year). Immune non-responders may be at risk of more
24 adverse COVID-19 related outcomes than HIV immune responders^{38,39,40,41}.
25
- 26
27 3. Multi-morbidity (defined as having ≥ 2 comorbidities). Comorbidities may include
28 cardiovascular disease (CVD) or CVD equivalents such as tobacco smoking. Other
29 comorbidities include CMV co-infection, hypertension, dyslipidemia, diabetes, chronic
30 obstructive pulmonary disease and obesity, as these are all common comorbidities
31 among PLWH^{2,42-45} and factors that contribute to worse outcomes with COVID-19.⁴⁶
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35 4. HIV-positive “stable” or “reference” group. These persons will have undetectable HIV
36 viral load for > 6 months, CD4 T cell counts > 350 cells/mm³, and a maximum of 1
37 comorbidity. To capture the full spectrum of individuals in the HIV-negative group, we
38 will include this HIV-positive “stable” group so that we can determine whether there are
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3 particular characteristics within PLWH which impact on immune response. In comparing
4 the stable and unstable groups, we will be able to determine whether participants with low
5 CD4 counts ($<350\text{cells}/\text{mm}^3$) differ in their response to vaccine from those with normal
6 CD4 T cell counts while controlling for other characteristics. We aim to enroll HIV-
7 negative and HIV-positive “stable” individuals with overlapping characteristics (i.e., some
8 should have multiple comorbidities) so that the groups are comparable.
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18 **General Methodology and participant timeline**

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21 Participants will attend 5 visits over 12 months: pre-vaccination; 1 month following first vaccine
22 dose; and at 3, 6 and 12 months following the second vaccine dose (**Table 1**). Each visit will last
23 between 20-60 minutes.
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29 **Primary Endpoint:** Percentage of PLWH with COVID-19-specific antibodies at 6 months
30 following 2nd vaccine dose.
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34 **Secondary Endpoints:** Percentage of individuals with 1) COVID-19 neutralization capacity at 6
35 months following 2nd vaccine dose and 2) COVID-19-specific antibodies at 12 months following
36 2nd vaccine dose. 3) Proportion and activation status of CD4 T cells, CD8 T cells, B cells, natural
37 killer cells and monocytes, pre-vaccination and 6 months post 2nd vaccine dose.
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44 **Exploratory Endpoints:** 1) COVID-19-specific antibodies at 6 months following 2nd vaccine dose,
45 stratified by subpopulations. Critically, we will also assess the ability of vaccine-elicited antibodies
46 to cross-recognize SARS-CoV-2 S protein variants, including N501Y and/or E484K, using in-
47 house assays.
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Sample size

Our primary outcome is the proportion of individuals in each group who mount a satisfactory immune response, although the best marker of what constitutes a satisfactory immune response is unclear at the moment and the science is rapidly evolving. We initially defined a successful immune response as a 4-fold relative rise in IgG production at 6 months.⁴⁷ We anticipated that 90% of HIV-negative individuals would mount an adequate IgG response at this timepoint^{27,34}, versus 70% of PLWH.^{12,48} If 20% of the sample were to have the characteristic of interest or predictor variable (e.g., 20% with multimorbidities), enrolling 200 PLWH and 50 HIV-negative participants would provide sufficient statistical power (>80%) to detect a 20% difference in outcomes between groups whatever the exact proportions. In addition, we calculated that we would have >80% power to detect a 20% difference in outcome between those with suppressed CD4 count or unsuppressed viral load and the HIV- group. Previous studies of temporal differences in humoral and cellular responses to COVID-19 have shown differences between individuals when sample sizes included 100 participants or fewer.⁴⁹⁻⁵³ We would also have >80% power to detect a 20% difference in outcome between the higher risk PLWH (ie, with CD4 counts <200 cells/mm³ and/or unsuppressed HIV viral load) and the HIV-negative group. Such recruitment targets would also also provide a sufficient buffer to account for potential drop-outs of 5-10%. However, to increase our ability to detect differences in our primary outcome between the four sub-populations of interest (individuals of older age; immune non-responders; persons with multimorbidity; and an HIV-positive “stable” or “reference” group), we plan to recruit 400 PLWH and use data from the *entire* cohort of HIV-negative individuals in the SSO study (approximately 1000 individuals) to increase power. Inevitably, the higher risk groups will be overlapping, so we will recruit a

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3 minimum of 20% of the 400 PLWH per category. By using the entire cohort of HIV-negative
4 individuals in the SSO study, we avoid the need to match PLWH and HIV-negative participants.
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10 **Recruitment**

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13 Participants will be informed about the study through a recruitment flyer during routine physician
14 visits to their HIV clinic and via established recruitment strategies through our community partners
15 and the CIHR Canadian HIV Trials Network (CTN) via webpages, email, and social media
16 platforms. Individuals followed for routine HIV care at clinics other than the 4 enrolment sites are
17 eligible to participate if they can come to the enrolment site for study visits. Participants will be
18 compensated \$40 per study visit to help offset the time commitment and parking fees. We will
19 make a concerted effort, through the use of recruitment quotas, to ensure the HIV-negative and
20 HIV-positive “stable” groups have overlapping characteristics (eg, age >55 years, CD4 count <350
21 cells/mm³, comorbidities) so that the groups will be comparable.
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37 **Data Collection**

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40 Medical history and HIV history will be gathered from both patient interviews and clinic chart
41 reviews following written informed consent. Information extracted will include comorbidities,
42 year of HIV diagnosis, CD4 T cell nadir (if known) in addition to tobacco smoking and cannabis
43 use history. Medications will be recorded in addition to the ART regimen. History of COVID-19
44 infection and date of confirmatory test will be recorded.
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51 **Sample Collection:** At each visit, blood will be collected to isolate serum, plasma and peripheral
52 blood mononuclear cells (PBMCs).
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3 ***Humoral Immunity (SARS-CoV-2 Binding Antibodies):*** We will evaluate levels of
4 immunoglobulins M and A (IgM, IgA) and IgG targeting the SARS-CoV-2 Spike (S) protein
5 receptor-binding domain (RBD) and nucleocapsid protein using a high-throughput automated
6 ELISA co-developed and validated by Dr Marc-Andre Langlois,⁵⁴ thereby distinguishing vaccine-
7 induced (S only) from infection-induced (S and nucleocapsid (N)) responses. We will also evaluate
8 samples for IgM and IgG antibody cross-recognition of RBD VoC, including those harbouring
9 *N501Y and/or E484K* (e.g., United Kingdom and South African strains, respectively) using a
10 multiplex ELISA assay developed by Dr Mark Brockman.⁵⁵ This assay can be rapidly adapted to
11 accommodate emerging variants. We will test plasma samples for their capacity to block viral
12 entry using a well-established neutralization assay based on retroviruses pseudotyped with the
13 SARS-CoV-2 S protein.^{49,51}

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29 ***Cellular Immunity:*** Flow cytometry will be performed to enumerate CD4 T cells (including helper
30 and regulatory subsets), CD8 T cells and other T cell subsets (including naïve, central memory,
31 transitional memory, effector memory and terminally differentiated cells), B cells (including naïve,
32 memory and antibody-secreting B cells), Natural Killer cells and monocytes (classical,
33 inflammatory and non-classical). We will also evaluate markers of cellular immune activation,
34 senescence and exhaustion. Following high-resolution Human Leukocyte Antigen class I/II typing,
35 we will examine COVID-19-specific T cell responses using an activation-induced marker (AIM)
36 assay. Briefly, PBMCs will be stimulated overnight with pools of SARS-CoV-2 S peptides.
37 Activated CD4 and CD8 T cells will be quantified by flow cytometry-based expression of CD137,
38 OX40 and/or CD69. Gene expression will be assessed by single-cell RNA sequencing of PBMC
39 as described previously.⁵⁶ T and B cell epitope specificity will be confirmed using virus-derived
40 antigens (peptide/HLA or RBD dextramers, respectively). Plasma levels of inflammatory markers
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3 including interferon (IFN)- γ , interleukin (IL)-1 β , IL-2, IL-4 IL-6, IL-8, IL-10, IL-13, IL-17,
4 transforming growth factor (TGF)- β , IFN- γ -induced protein-10 (IP-10), IL-12p70 and tumour
5 necrosis factor (TNF)- α will be measured using multiplex Luminex assays, D-dimer, C-reactive
6 protein, and markers of microbial translocation lipopolysaccharide (LPS), beta-d-glucan (β dG) and
7 soluble CD14 will be evaluated by ELISA.⁵⁷
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21 **Exploratory Safety and Tolerability of COVID-19 Vaccines in PLWH**

22 In the prospective cohort, we will explore vaccine safety and efficacy to inform subsequent studies.

23 Reactogenicity: **Symptoms Diary:** Participants will be asked to document specific local and
24 systemic reactions in a diary for 1 week and 1 month following each injection, as was done in
25 Pfizer-BioNTech Phase 3 studies.⁴⁷ We will report the proportion of participants developing local
26 (redness, pain or swelling at the injection site) or systemic effects (fatigue, headache, muscle pain,
27 fever, joint pain, diarrhea) within 7-30 days following each vaccine dose with 95% confidence
28 intervals (Supplementary information).
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39 **COVID-19 Questionnaires:** We will administer the COVID-19 System Questionnaire to
40 participants who develop a flu-like illness to confirm the illness, along with PCR-based tests for
41 COVID-19. Participants will complete the COVID-19 Immunity Task Force (CITF) Standardized
42 Core Survey Data Elements questionnaire prior to vaccination and a modified CITF questionnaire
43 (minus the demographic information) at follow-up visits (Supplementary information).
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51 If participants develop COVID-19 symptoms 14 days+ after vaccination, we will also collect CITF
52 system questionnaire (length of illness and symptomatology, which vaccine was administered,
53 number of doses vaccine received) and saliva specimens to enable study of COVID-19 variants of
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3 concern. ([https://www.covid19immunitytaskforce.ca/covid-19-immunity-task-force-releases-](https://www.covid19immunitytaskforce.ca/covid-19-immunity-task-force-releases-standardized-core-survey-data-elements/)
4 [standardized-core-survey-data-elements/](https://www.covid19immunitytaskforce.ca/covid-19-immunity-task-force-releases-standardized-core-survey-data-elements/))
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10 **Data management**

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13 The study sponsor, the CTN, will be responsible for national project management, database
14 development, data management and data analysis. To facilitate data sharing, we will: 1) use
15 standard encodings for CITF-defined Core Data Elements; 1) request immunogenicity study
16 participants consent to data sharing as guided by the CITF, including collecting survey elements
17 and saliva 14+ days after vaccination on symptomatic participants to determine whether the
18 infecting strain is a COVID-19 VoC and 3) rapidly share interim data and all requested study
19 metadata for cataloguing.
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31 **Confidentiality**

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34 All participant-related information, including Case Report Forms, laboratory specimens,
35 evaluation forms and reports, will be kept strictly confidential. All records will be held in a secure,
36 locked location and only accessible to research staff. Participants will be identified using a coded
37 number specific to each participant. All computerized databases will identify participants by
38 numeric codes only and will be password protected. Upon request, and in the presence of the
39 investigator or his/her representative, participant data will be made available to the study sponsor,
40 monitoring groups representative of the study sponsor, representatives of funding groups, and
41 applicable regulatory agencies to verify clinical study procedures and/or data, as is permissible by
42 local regulations.
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Statistical Analyses

We will use regression techniques to compare COVID-19-specific immune responses applying data transformation where necessary to conform with distributional assumptions in order to determine whether there are differences between the “unstable” (CD4<350) PLWH group, the stable PLWH cohort and the HIV- controls, controlling for factors that are believed to be associated with immune response. We will also perform unadjusted analyses to determine whether there are differences which may or not be driven by factors associated with group membership. We will report data from exploratory analyses with descriptive statistics and data for vaccines from different manufacturers separately and combined. We will stratify results by the number of doses received and the time interval between the two doses in case these factors drive response and differ between groups. We will stratify immunogenicity data by sex as females and males have differences in both vaccine-elicited immune responses⁵⁸ and adverse effects from vaccines.⁵⁹ Furthermore, we will stratify analyses by individuals who are naive to COVID-19 versus those with pre-existing antibodies as a result of prior COVID-19 infection. This will be important since antibody responses (particularly after the 1st dose) will be much higher in convalescent individuals,^{60,61} so it is not appropriate to include them with individuals who do not have pre-existing antibodies to COVID-19.

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

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3 Written informed consent will be obtained from all study participants. The study will be
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5 conducted in accordance with the Declaration of Helsinki. At the time of manuscript
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7 preparation, a very closely related protocol has been approved by the University of British
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9 Columbia/Providence Health Care Research Institute and Simon Fraser University Research
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11 Ethics Boards. The present protocol is under review by the Research Institute of the McGill
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13 University Health Centre (2nd review), the Ottawa Hospital Research Ethics Board, the
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15 University of Toronto Research Ethics Board. Patient enrollment for this trial is anticipated
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17 to begin June 2021.
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25 **Availability of data and materials**

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28 De-identified participant data will be stored on a secure password-protected RedCap database.
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30 Access to the database will be controlled by the CTN. Access to the final study database will be
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32 provided upon written reasonable request to the corresponding author/principal investigator
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34 following publication and CTN and CITF approval.
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40 We will standardize reagents and analysis strategies, where possible, working with the Immune
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42 Sciences Network and Testing Working Party recommendations to enable data sharing and avoid
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44 duplication in consultation with other CIHR and CITF-funded vaccine surveillance projects. We
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46 will also contribute results to SeroTracker, a knowledge hub that tracks and synthesizes findings
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48 from SARS- CoV-2 serosurveillance efforts worldwide
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50 (<https://www.covid19immunitytaskforce.ca/serotracker/>). To inform COVID-19 immunization
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52 guidelines and future interventions for PLWH in Canada and internationally, we are committed to
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3 sharing results with all stakeholders and will adhere to Wellcome's *Sharing research data and*
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7 *findings relevant to the novel coronavirus (COVID-19) outbreak* statement.⁶²
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16 **Knowledge Translation (KT) & Dissemination Plan**

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19 Serology results will be provided to individual study participants at the end of the study, along
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22 with a summary of study results and their implication in lay language. We prioritize meaningful
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25 community engagement and our Community Advisory Committee includes PLWH and
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27 representation from the Canadian Aboriginal AIDS Network. The Community Advisory
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30 Committee reviews protocols and informed consent forms and advises on community priorities.
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34 Our well-established relationship with CATIE, Canada's source for HIV information, will enhance
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KT. We will leverage our KT staff to share lay language updates via press releases, media
coverage, website, e-newsletters and social media and undertake targeted KT activities to mobilize
knowledge across our network and report results to senior policymakers, via research summaries
and policy briefs, and community groups and participants, via factsheets. Our team will publish
manuscripts, contribute to guidelines, and present to stakeholders.

Patient and Public Involvement

The CTN Community Advisory Committee (CAC) was involved in the peer review process of this study proposal and deemed that the research questions addressed were of very high priority to PLWH. The CAC's critiques of the initial proposal were taken into account in the revised proposal. Two members of the CAC (SM and EM) were involved in finalizing the study design, inclusion/exclusion criteria, outcome measures and monitoring plans and are formal study investigators and co-authors. Community consultants will receive financial compensation to recognize their time commitment and expertise.

DISCUSSION

Herein, we present the protocol for an observational cohort study to evaluate COVID-19 vaccine-elicited immunogenicity in PLWH, with a priority of determining immunogenicity in PLWH who are of older age, immune non-responders and those with multimorbidity. These 3 groups were selected since they represent subpopulations most likely to experience poor outcomes following COVID-19 infection and have a weaker immune response to vaccination.

PLWH immune non-responders are at risk of more adverse COVID-19 related outcomes than HIV immune responders. In the study performed by Braunstein *et al.*, PLWH with COVID-19 infection had a higher proportion of hospital admissions, intensive care unit (ICU) admission and death. Those who experienced these COVID-19-related outcomes had CD4 T cell counts below 500

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3 cells/mm³.^{3,38} Similarly, the study by Dandachi *et al.* found that having CD4 T cell counts below
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5 200 cells/mm³ was associated with severe outcomes such as ICU admission, intubation and
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7 death.³⁹ Furthermore, a multicentre cohort study by Hoffman *et al.* showed that CD4 T cell counts
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9 <350 cells/mm³ were associated with severe COVID-19 (adjusted OR 2.85, 95% CI 1.26-6.44).⁴⁰
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12 However, in a group of patients with inborn errors of immunity, Kinoshita *et al.* they demonstrated
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14 robust T cell activity and humoral immunity against COVID-19 structural proteins in some
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16 patients with antibody deficiency,⁶³ underscoring the heterogeneity and complexity of immune
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18 response.
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25 A major challenge with planning this study is the unprecedented, rapidly-changing nature of the
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27 COVID-19 pandemic and evolving scientific information. As a result, data on the optimal time
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29 points to assess immune responses post COVID-19 vaccination administration are rapidly
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31 changing, resulting in multiple adjustments in our protocol plans. Within Canada, the vaccination
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33 schedule is determined by the provinces with input from NACI. However, differences exist
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35 between provinces regarding to vaccine supply, eligibility criteria, type of vaccine administered
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37 and time period between vaccine doses. We are mitigating these challenges by holding monthly
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39 meetings with teams to discuss these issues over the previous month, troubleshoot and adjust
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41 recruitment priorities accordingly for the upcoming month. Ideally, and under non-pandemic
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43 circumstances, we would establish, a priori, methods for analyzing data from single vs. two-dose
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45 vaccines. However, in the current context with uncertainty of vaccine supply and distribution, such
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47 detailed plans are impractical and will depend on the methods of vaccination used in the
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49 participants enrolling in this study. This statement holds true for other variables we will likely
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51 encounter, such as different dosing intervals amongst persons receiving two-dose vaccines.
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7 The importance of advanced age in impaired vaccine-induced immunogenicity is well-
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10 documented. Due to a combination of disrupted in posttranscriptional regulation, T cell receptor
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13 signalling, and metabolic function, older individuals demonstrate reduced quantity and
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16 functionality of T-cells^{64,65}. When this balance is disrupted, T-cells exhibit shorter-lived effector
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19 phenotypes rather than memory or follicular helper T cells and vaccine-induced antibodies are less
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22 protective than in younger persons^{64,65}. As the elderly are considered a priority vaccination group,
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26 many of them were eligible for vaccination in early 2021 in Canada, before this current study
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29 began, meaning that baseline plasma, serum and PBMCs will not be available for participants in
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32 this subpopulation of interest. Another drawback with starting this study in May 2021 is that we
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35 may miss other important groups of PLWH, including Indigenous persons who were prioritized as
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38 high-risk populations for immunization and were eligible to receive COVID-19 vaccines at a
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41 younger age than the general population.
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46 Another major challenge with the planning of this study was the need to ensure an adequate sample
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48 size to meet the primary objective in the group as a whole, but also in important subpopulations of
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50 PLWH. Enrollment of such a large number of individuals, with follow-up until 12 months
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52 following the second vaccine dose, is very resource-intensive and requires dedicated study
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54 participants. We will provide individualized antibody results to participants at study completion to
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3 increase study engagement and prevent drop-outs. Furthermore, due to the need to rapidly enroll
4 participants to match the pace of the COVID-19 vaccine rollout, we decided to use CTN study
5 sites with large clinic volumes and proven capacity to recruit. However, these clinics are based in
6 urban centres and, therefore, may follow individuals who differ systematically from PLWH
7 followed outside of the cities. PLWH who live in cities may be of higher socioeconomic status and
8 consist of more men who have sex with men (MSM). Therefore, each site will need to make a
9 concerted effort to recruit sufficient participants with other profiles. For this reason, we will
10 employ a flexible recruitment strategy, whereby sites that can recruit the required participants with
11 characteristics of interest more easily than other sites can help to make up for lower recruitment
12 flexibility at other sites. As with many studies, recruitment of women living with HIV may be
13 challenging. Due to our connection with other studies within the CTN and the help of our
14 community advisory board, we are encouraging clinics with predominantly female clients to
15 ensure they inform their female patients living with HIV about this study.
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36 Currently, the immune correlate of protection against COVID-19 is undefined. T cell and B cell
37 responses are usually used as surrogates of protection.⁶⁶ We decided to use a 4-fold rise from
38 baseline in IgG production following second vaccine dose as the criteria for a successful vaccine
39 response, as was indicated in the Pfizer study⁴⁷, in order to calculate our sample size. Data from
40 the Pfizer study submitted to the Food and Drug Administration and published by Walsh *et al.*,
41 report geometric mean titers that were compared to those from a human SARS-CoV-2
42 convalescent serum panel as a benchmark. Increased titers were expressed in logarithmic fold
43 increases.⁶⁷ There are currently no national standards for presenting the serology data. Some
44 groups prefer to report the raw signal values, whereas others normalize data as fold increases.
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3 Since individual baseline values will not be available for participants who have already received
4 their first vaccine dose, one option is to use the cohort baseline data derived from non-vaccinated
5 participants. Alternatively, we may opt to examine relative titers, or fold-changes, and therefore
6 baseline data will not actually be required. Since science is continuously evolving, we will use the
7 definition of a successful vaccine response which is most widely accepted at the time of
8 publication.
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20 The best methodology to match PLWH with the HIV-negative group remains unclear. As
21 discussed by Wong *et al.*, the ideal comparison group would be individuals who are identical to
22 HIV-negative adults in all aspects except HIV status⁶⁸. As PLWH have distinct characteristics,
23 traditional risk factors, lifestyle factors and socioeconomic factors compared to the general
24 population, the general population may not be the ideal comparison group⁶⁸. Differences include
25 increased tobacco smoking⁶⁹, substance use⁷⁰ and comorbidities⁷¹ amongst PLWH compared to
26 the general population. However, PLWH also undergo more screening for age-related
27 comorbidities due to frequent contact with health care providers⁶⁸. We plan to match PLWH
28 participants with HIV-negative individuals from the SSO study. As previously mentioned, as long
29 as we ensure there are 20% of individuals with the characteristics of interest in the HIV-negative
30 and HIV-positive “stable” cohorts, we can compare groups while controlling for these
31 characteristics via regression.
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48 Taken together, the findings from this study will provide valuable insight into COVID-19-vaccine-
49 induced immunogenicity in important sub-populations of PLWH. HIV-positive persons of older
50 age, with CD4 counts <350 cells/mm³ and multimorbidity were not included in the early clinical
51 trials, yet are most likely to suffer from poor outcomes if infected with COVID-19. These findings
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will inform clinical guideline recommendations for PLWH and, in turn, reduce COVID-19-induced morbidity and mortality.

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18 **Authors' contributions**

19
20 Co-principal investigators of the study are CTC, CLC and AA. CC and CLC conceived the study,
21 led the proposal and protocol development. CC wrote the first draft of the manuscript. JS is the
22 biostatistician who provided methodological expertise and performed sample size calculations. All
23 other authors contributed to protocol development, study design and development of the proposal.
24
25 CTC, MAL, MAJ, MO, MB, and ZB designed the laboratory evaluations. MAL will be responsible
26 for studies on humoral immunity. MAJ will be responsible for flow cytometric studies to define
27 proportions of immune cells and their subsets, while CTC will be responsible for cytokine
28 assessment. MAB and ZLB will be responsible for RNA profiling. MAL and MAB will perform
29 the analysis of antibodies to COVID-19 variants. MO and MAB will perform analyses of T cell
30 responses to vaccine immunogens. Markers of gut barrier damage, microbial translocation and
31 CMV IgG titers will be performed by JPR. HLA typing will be performed as necessary for
32 participants evaluated for T cell responses by MO, ZLB and MB. JS will oversee data analysis
33 between groups and subgroup analyses. All authors critically reviewed and approved the final
34 manuscript.
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44 **Competing interests**

45
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47 The authors declare that they have no competing interests
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For peer review only

Table 1: Visits and Procedure Schedule

Visit number	1 ¹ (Screen)	Vaccine	2	Vaccine	3 ⁶	4 ⁶	5 ⁶
Week Number	-12 to 0 weeks	0	4 weeks		3 mo after dose 2	6 mo after dose 2	12 mo after dose 2
Window	-3 mo						
Inclusion/Exclusion	X		X				
Informed Consent	X						
Medical History	X						

Blood Draw: Immunology ²	X		X		X	X	X
Blood Draw: CD4/Viral Load ³	X		X		X	X	X
Vaccination ⁴		X		X			
Participant Diary ⁵		X	X	X	X		
CITF ⁷ Questionnaire	X		X		X	X	X
Adverse Events ⁸			X		X		
Concomitant Meds	X		X		X	X	X

¹Screening assessment may be performed same day as vaccination but will be completed prior to vaccination.

²Immunoglobulin levels flow cytometry and cytokine secretion (immunogenicity measures); Will be collected at each visit. For participants who have already received a vaccine dose prior to study enrolment, “baseline” immunoglobulin levels (i.e., pre-vaccination) may not be available.

³Blood work such as CD4 and Viral load can be collected as part of standard of care

⁴Participants will receive the COVID-19 vaccine outside of the study per standard of care as part of their provincial immunization program.

⁵Participants will maintain a diary after vaccination during which they will record their vaccine reactions, oral temperature and any febrile respiratory tract symptoms as well as general changes to health and medications. The diary will be evaluated up to 30 days following each injection.

⁶Visits 3, 4, 5 will be conducted at 3, 6, 12 months after dose 1 respectively, for COVID-19 vaccines administered as a one-dose schedule.

⁷The full CITF questionnaire will be completed at visit 1 and the modified CITF questionnaire will be completed at subsequent visits.

1
2
3 ⁸Adverse events will only be collected at 7 and 30 days post vaccination and for
4 participants who receive a vaccine while currently enrolled in the study (i.e. adverse
5 events will not be collected retrospectively)
6
7

8
9
10 For participants who develop COVID19-symptoms 14+ days following vaccination.

11
12 Participants will be asked to complete the COVID-19 Symptom Survey (Supplementary
13 materials) and to go for a COVID-19 test at their nearest test centre and notify the study
14 staff of their test result. If positive for COVID-19, the study staff will mail the participant
15 6 saliva collection kits by courier in order to collect information on SARS-CoV-2
16 variants
17
18

19
20
21 Participants who have already received 1 vaccine dose: These individuals may be
22 enrolled in the study, at any duration of time post first dose, as long as the baseline blood
23 draw is before the second booster. Visits 1 and 2 will be combined.
24
25

26
27
28 Participants who have already received 2 vaccine doses: These individuals must be
29 enrolled in the study within 3 months of their 2nd dose. Visits 1 and 3 will be combined
30 and Visit 2 will not be required. Participants will follow-up at visits 4 and 5.
31
32



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DATA COLLECTION
 WORKSHEET

Participant ID

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Vaccine 1

Vaccine 2

COVID-19 SYMPTOMS QUESTIONNAIRE

Have you experienced any of the following COVID-19 signs or symptoms?

Sign	Yes	No	If yes, provide date, time
Fever, chills			
Cough			
Shortness of breath			
Acute loss of smell or taste			
Fatigue			
Headache			
Muscle aches			
Nausea/Vomiting/Diarrhea			
General weakness			
Nasal congestion			
Sore throat			



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WORKSHEET

Participant ID

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- Vaccine 1
- Vaccine 2

PARTICIPANT DIARY

Following each injection of COVID-19 vaccine, please indicate whether you experienced any of the following, within 7 days and within 30 days, and indicate the severity. See the Other Signs or Symptoms worksheet for a guide to the severity levels.

	Date:	Date:	Date:	Date:	Date:	Date:	Date:	Date:	
Sign or Symptom	Day 0*	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Within 30 days
Pain at injection site									
Redness									
Swelling									
Lymphadenopathy/Axillary swelling and tenderness									
Fatigue									
Headache									
Muscle Pain									
Chills									
Joint pain									
Fever									
Diarrhea									
Nausea and/or Vomiting									

* Day 0 refers to day vaccine received, Day 1 is the *following day*, and so forth



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CTN 328: HIV-COV

CITF CDE BASELINE QUESTIONNAIRE

This version is only administered at Screening
Please answer all questions unless otherwise indicated

Participant ID: _____

Section 1: Demographics

1. Date (DD-MMM-YYYY):

____ / ____ / _____

2. What is your age?

_____ YRS _____ MO OR Prefer not to answer

3. What was your assigned sex at birth?

- Male
 Female
 Prefer to self-describe (specify) _____
 Prefer not to answer

4. What is your sex now?

- Male
 Female
 Prefer to self-describe (specify) _____
 Prefer not to answer

1
2
3 5. What is your gender (how do you currently self-identify)?
4

- 5 Male
6 Female
7 Non-binary, genderqueer, agender or a similar identity
8 Two-spirit
9 Prefer to self-describe (specify) _____
10 Prefer not to answer
11
12

13 6. Are you an Indigenous person originating from North America?
14

15 [If NO or Prefer not to answer, please proceed to Q9](#)

- 16 No
17 Yes
18 Prefer not to answer
19
20

21 7. Which of the following groups do you belong to? Please select all that apply.
22

23 [Only answer if Q6 = YES](#)

- 24 First Nations
25 Inuit
26 Metis
27 Non-status First Nations
28 Other Indigenous (specify) _____
29 Prefer not to answer
30
31
32

33 8. Do you live on reserve?
34

35 [Only answer if Q7 = First Nations](#)

- 36 Yes
37 No
38 Prefer not to answer
39
40

41 9. How would you describe your ethnicity or race? Please select all that apply.
42

43 If you are an Indigenous person and answered YES to Q6, select any other that apply.
44

- | | |
|---|--|
| 45 <input type="checkbox"/> White | <input type="checkbox"/> West Asian |
| 46 <input type="checkbox"/> South Asian | <input type="checkbox"/> Korean |
| 47 <input type="checkbox"/> Chinese | <input type="checkbox"/> Japanese |
| 48 <input type="checkbox"/> Black | <input type="checkbox"/> Prefer to self-describe (specify) |
| 49 <input type="checkbox"/> Filipino | _____ |
| 50 <input type="checkbox"/> Latin American | <input type="checkbox"/> Prefer not to answer |
| 51 <input type="checkbox"/> Arab | |
| 52 <input type="checkbox"/> Southeast Asian | |
| 53 | |
| 54 | |
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| 57 | |
| 58 | |

1
2
3 10. What are the first three digits of your postal code?
4

5 _____ OR Prefer not to answer
6
7

8
9 11. What is the highest level of education you have completed?
10

- 11 Less than high school graduation
12 High school graduation
13 Trade certificate, vocational school, or apprenticeship training
14 Non-university certificate or diploma from a community college, CEGEP
15 University Bachelor's degree
16 University graduate degree (Master's, Doctorate, etc.)
17 Prefer not to answer
18
19

20 12. How many people live in your household, including yourself?
21

22 _____ OR Prefer not to answer
23
24

25
26 13. How many bedrooms are in your household?
27

28 _____ OR Prefer not to answer
29
30

31
32 14. How many bathrooms are in your household?
33

34 _____ OR Prefer not to answer
35
36

37
38 **Section 2: COVID-19**

39 15. Do you think you have had COVID-19?
40

41 [If NO or Prefer not to answer, please proceed to Q18](#)
42

- 43 No
44 Yes
45 Prefer not to answer
46
47
48
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1
2
3 16. Why do you think you have had COVID-19? Please select all that apply.
4

5 [Only answer if Q15 = YES](#)

- 6
7 Symptom review online
8 Symptom profile
9 Nasal/throat test result
10 Health care provider
11 Contact with case
12 Other (specify) _____
13 Prefer not to answer
14
15

16 17. Were you hospitalized due to COVID-19?
17

18 [Only answer if Q15 = YES](#)

- 19
20 No
21 Yes
22 Prefer not to answer
23

24 18. Have you ever been tested for an active COVID-19 infection (using nasopharyngeal/throat swab, saliva, or
25 gargle test)?
26

27 [If NO or Prefer not to answer, please proceed to Q21](#)

- 28
29 No
30 Yes
31 Prefer not to answer
32
33

34 19. If yes, how many times have you been tested?
35

36 [Only answer if Q18 = YES](#)

37 _____ OR Prefer not to answer
38

39 20.1 Answer the following questions about the **first COVID-19 test**, if applicable.
40

41 20.1.a What was the date of the **first** test?
42

43 _____ DD / _____ MO / _____ YR
44

45 20.1.b What was the result of the **first** test?
46

- 47 Negative
48 Positive
49 Don't know
50
51
52
53
54
55
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58

1
2
3 20.1.c Did you have any symptoms of COVID when you had this test?
4

- 5 No
6 Yes
7 Don't know
8

9
10 20.1.d If yes, what symptoms did you have?
11

12 [Only answer if Q20.1.c = YES](#)
13

- 14 Cough
15 Fever
16 Shortness of breath
17 Sore muscles
18 Headache
19 Sore throat
20 Diarrhea
21 Decreased sense of smell or taste
22 Other (specify) _____
23
24
25

26
27 20.2 Answer the following questions about the **second COVID-19 test**, if applicable.

28 20.2.a What was the date of the **second** test?
29

30 _____ DD / _____ MO / _____ YR
31

32 20.2.b What was the result of the **second** test?
33

- 34 Negative
35 Positive
36 Don't know
37

38 20.2.c Did you have any symptoms of COVID when you had this test?
39

- 40 No
41 Yes
42 Don't know
43
44
45
46
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1
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3 20.2.d If yes, what symptoms did you have?
4

5 [Only answer if Q20.2.c = YES](#)
6

- 7
8 Cough
9 Fever
10 Shortness of breath
11 Sore muscles
12 Headache
13 Sore throat
14 Diarrhea
15 Decreased sense of smell or taste
16 Other (specify) _____
17
18
19

20 20.3 Answer the following questions about the **third COVID-19 test**, if applicable.

21 20.3.a What was the date of the **third** test?
22

23 _____ DD / _____ MO / _____ YR
24

25 20.3.b What was the result of the **third** test?
26

- 27 Negative
28 Positive
29 Don't know
30

31 20.3.c Did you have any symptoms of COVID when you had this test?
32

- 33 No
34 Yes
35 Don't know
36
37

38 20.3.d If yes, what symptoms did you have?
39

40 [Only answer if Q20.3.c = YES](#)
41

- 42
43 Cough
44 Fever
45 Shortness of breath
46 Sore muscles
47 Headache
48 Sore throat
49 Diarrhea
50 Decreased sense of smell or taste
51 Other (specify) _____
52
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1
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3 20.4.a Have you **tested positive** for COVID-19 (using nasopharyngeal, throat swab, saliva or gargle test) on a
4 test that wasn't included the questions above (that is, on the **4th or later test**)?
5

6 [If NO, please proceed to Q21](#)

- 7
8 No
9 Yes
10

11 20.4.b If yes, what was the date the first time you tested positive?

12
13 [Only answer if Q20.4.a = YES](#)

14
15 ____ DD / ____ MO ____ YR
16
17

18
19 **Section 3: Exposure**

20
21 21.a Have you traveled outside of your home province since **January 2020**?

22 [If NO, please proceed to Q23](#)

- 23
24 No
25 Yes
26 Prefer not to answer
27

28
29 21.b If you think you had COVID, did you travel in the 6 months before your symptoms began?

30 [Only answer if Q15 = YES](#)

- 31
32 No
33 Yes
34 Prefer not to answer
35
36
37
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22. What province(s)/territory(ies) or country(ies) did you travel to? Select all that apply.

Only answer if Q21.a or Q21.b = YES

- Alberta
 British Columbia
 Manitoba
 New Brunswick
 Newfoundland and Labrador
 Northwest Territories
 Nova Scotia
 Nunavut
 Ontario
 Prince Edward Island
 Quebec
 Saskatchewan
 Yukon

OR Prefer not to answer

List countries you travelled to (separated by a comma):

23.a Do you do either paid or unpaid work in an environment where you work in close proximity to other people?

If NO or Prefer not to answer, please proceed to Q24

- No
 Yes
 Prefer not to answer

23.b If yes, have you been working in any of the following occupations or worksites in the past year? Please select all that apply.

Only answer if Q23.a = YES

- | | |
|---|--|
| <input type="checkbox"/> Hospital or health care facility | <input type="checkbox"/> Pharmacy |
| <input type="checkbox"/> First responder (paramedic/firefighter/police officer) | <input type="checkbox"/> Hairdresser or barber |
| <input type="checkbox"/> Childcare worker | <input type="checkbox"/> Aesthetician |
| <input type="checkbox"/> Correctional officer | <input type="checkbox"/> Flight attendant |
| <input type="checkbox"/> Teacher or other school staff | <input type="checkbox"/> Factor worker |
| <input type="checkbox"/> Transit driver | <input type="checkbox"/> Other (specify) |
| <input type="checkbox"/> Food service industry | <input type="checkbox"/> _____ |
| <input type="checkbox"/> Grocery store | <input type="checkbox"/> Prefer not to answer |

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3 24.a How many times have you been in a gathering of 10 or more since **March 2020**?

4 _____ OR Prefer not to answer

5
6
7 24.b If you think you have had COVID, how many times were you in gatherings of more than 10 people in the 6
8 months before your symptoms began?

9
10 [Only answer if Q15 = YES](#)

11 _____ OR Prefer not to answer

12
13
14
15
16 **Section 4: Health and Health Behaviours**

17 25. Do you currently smoke tobacco?

- 18
19 No
20 Yes
21 Prefer not to answer
22
23

24 26. If yes, how often do you smoke tobacco?

25
26 [Only answer if Q25 = YES](#)

- 27 Less than daily
28 Daily
29
30

31 27. Do you currently use e-cigarettes (vape)?

- 32 No
33 Yes
34 Prefer not to answer
35
36

37 28. If yes, how often do you use e-cigarettes (vape)?

38
39 [Only answer if Q27 = YES](#)

- 40 Less than daily
41 Daily
42
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29. Have you been diagnosed by a physician with any of the following chronic medical conditions? Please provide an answer for each condition.

		Yes	No	Don't Know	Prefer not to answer
a.	Hypertension				
b.	Diabetes				
c.	Asthma				
d.	Chronic Lung Disease				
e.	Chronic Heart Disease				
f.	Chronic Kidney Disease				
g.	Liver Disease				
h.	Cancer				
i.	Chronic Blood Disorder				
j.	Immune Suppressed				
k.	Chronic Neurological Disorder				

30. What is your current weight (circle units)?

_____ kg / lbs OR Prefer not to answer

31. What is your current height?

____ . ____ m OR ____ ft ____ in OR Prefer not to answer

32. Do you have a family physician/primary care provider?

- No
 Yes
 Don't know
 Prefer not to answer

33. Do you usually get a flu shot?

- No
 Yes
 Prefer not to answer

34. Indicate if, or how often you have done the following since **March 2020**?

		Never	Rarely	Occasionally	Often	Always	Prefer not to answer	
a.	Worn a mask in public places							
b.	Practiced physical distancing in public places							
c.	Avoided crowded places/gatherings							
d.	Avoided common greetings (such as a handshake or hug)							
		Never	Rarely	Occasionally	Often	Always	N/A	Prefer not to answer
e.	Limited contact with people at higher risk (e.g., an elderly relative)							
		No	Yes	N/A		Prefer not to answer		
f.	Self-isolated because you thought you were infected with COVID-19							
g.	Self-quarantined because you may have been exposed to COVID-19, but did not show symptoms							

35. **If you think you have had COVID**, have you done the following in the **6 months before your symptoms began?** (indicate how often).

Only answer if Q15 = YES

		Never	Rarely	Occasionally	Often	Always	N/A	Prefer not to answer
a.	Worn a mask in public places							
b.	Practiced physical distancing in public places							
c.	Avoided crowded places/gatherings							
d.	Avoided common greetings (such as handshake or hug)							
e.	Limited contact with people at higher risk (e.g., an elderly relative)							
		No	Yes	N/A		Prefer not to answer		
f.	Self-isolated because you thought you were infected with COVID-19							
g.	Self-quarantined because you may have been exposed to COVID-19, but did not show symptoms							

Section 5: Vaccine

36. Have you been vaccinated against COVID-19? Answer YES if you have received at least one dose of the COVID-19 vaccine.

[If NO or Prefer not to answer, proceed to Q43](#)

- No
- Yes
- Prefer not to answer

37. How many doses of the COVID-19 vaccine have you received so far?

[Only answer if Q36 = YES](#)

- One
- Two
- More than two

38. When did you receive the **first dose** of the COVID-19 vaccine?

[Only answer if Q36 = YES](#)

____ DD / ____ MM / _____ YR

39. When did you receive the **second dose** of the COVID-19 vaccine?

[Only answer if Q37 = TWO or MORE THAN TWO](#)

____ DD / ____ MM / _____ YR

40. Which vaccine did you receive?

[Only answer if Q36 = YES](#)

- Pfizer and BioNTech mRNA vaccine
- Moderna mRNA vaccine
- AstraZeneca Oxford vaccine
- Other (specify) _____
- Janssen (Johnson & Johnson) vaccine
- Don't know
- Prefer not to answer

41. Were you pregnant when you received the vaccine?

[If NO or N/A, proceed to Q43](#)

- No
- Yes
- N/A

42. If yes, what trimester were you in when you received the vaccine?

Only answer if Q41 = YES

- First
 Second
 Third

Section 6: Cannabis Use

43. Have you used cannabis (even once) in the past 12 months?

If NO, proceed to the end of this questionnaire

- No
 Yes

43.a If yes, how do you use cannabis? Please check all that apply.

Only answer if Q43 = YES

	Yes	No
Smoked dried plant		
Vaporized		
Oil		
Pills		
Added to baked good or other foods		
Other (specify)		

43.b If you smoke cannabis, please specify how you smoked/took cannabis:

- I do not smoke cannabis (proceed to Q44)

	Yes	No
Smoked as joint		
Smoked as joint mixed with tobacco		
Smoked as pipe		
Smoked as water pipe (bong)		
Inhaled using a vaporizer		
Eaten (e.g. as brownies, cake, cookies, etc.)		
Other (specify)		

1
2
3 44. Which response **best** describes how often you **currently** use cannabis?
4

5 [Only answer if Q43 = YES](#)

- 6
7 Rarely (2-3 times a year)
8 Monthly
9 Weekly
10 Daily
11 More than once a day
12

13
14 45. How many grams per week do you consume?

15 [Only answer if Q43 = YES](#)

- 16
17 Less than 1 gram
18 1-5 grams
19 6-9 grams
20 10 or more grams
21 Unknown
22
23

24 46. If you smoke cannabis, on average how many joints/cigarettes do you smoke per day?
25

26 [Only answer if Q43 = YES](#)

27 _____ OR I do not smoke cannabis
28
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33 **END OF QUESTIONNAIRE**
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the CTN
CIHR Canadian
HIV Trials Network

le Réseau
Réseau canadien
pour les essais VIH des IRSC

CTN 328: HIV-COV

CITF CDE FOLLOW-UP QUESTIONNAIRE

This version is administered at Visits 2, 3, 4, 5, and at unscheduled visits

Please answer all questions unless otherwise indicated

Participant ID: _____

1. Date (DD-MMM-YYYY):

___ / ___ / _____

Section 1: COVID-19

2. Do you think you have had COVID-19 since your last visit?

[If NO or Prefer not to answer, please proceed to Q5](#)

- No
 Yes
 Prefer not to answer

3. Why do you think you have had COVID-19 since your last visit? Please select all that apply.

[Only answer if Q2 = YES](#)

- Symptom review online
 Symptom profile
 Nasal/throat test result
 Health care provider
 Contact with case
 Other (specify) _____
 Prefer not to answer

1
2
3 4. Since your last visit, have you been hospitalized due to COVID-19?
4

5 [Only answer if Q2 = YES](#)

- 6
7 No
8 Yes
9 Prefer not to answer
10

11
12 5. Since your last visit, have you been tested for an active COVID-19 infection (using nasopharyngeal/throat
13 swab, saliva, or gargle test)?
14

15 [If NO or Prefer not to answer, please proceed to Q8](#)

- 16
17 No
18 Yes
19 Prefer not to answer
20

21
22 6. If yes, how many times have you been tested since your last visit?
23

24 [Only answer if Q5 = YES](#)

25 _____ OR Prefer not to answer
26
27
28
29

30 7.1 Answer the following questions about the **first COVID-19 test since your last visit**, if applicable.
31

32 7.1.a What was the date of the **first** test?
33

34 _____ DD / _____ MO / _____ YR
35

36 7.1.b What was the result of the **first** test?
37

- 38 Negative
39 Positive
40 Don't know
41

42 7.1.c Did you have any symptoms of COVID when you had this test?
43

- 44 No
45 Yes
46 Don't know
47
48
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1
2
3 7.1.d If yes, what symptoms did you have?
4

5 Only answer if Q7.1.c = YES
6

- 7
8 Cough
9 Fever
10 Shortness of breath
11 Sore muscles
12 Headache
13 Sore throat
14 Diarrhea
15 Decreased sense of smell or taste
16 Other (specify) _____
17
18
19
20

21
22 7.2 Answer the following questions about the **second COVID-19 test since your last visit**, if applicable.

23 7.2.a What was the date of the **second** test?
24

25 _____ DD / _____ MO / _____ YR
26

27 7.2.b What was the result of the **second** test?
28

- 29 Negative
30 Positive
31 Don't know
32

33 7.2.c Did you have any symptoms of COVID when you had this test?
34

- 35 No
36 Yes
37 Don't know
38
39

40 7.2.d If yes, what symptoms did you have?
41

42 Only answer if Q7.2.c = YES
43

- 44 Cough
45 Fever
46 Shortness of breath
47 Sore muscles
48 Headache
49 Sore throat
50 Diarrhea
51 Decreased sense of smell or taste
52 Other (specify) _____
53
54
55
56
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7.3 Answer the following questions about the **third COVID-19 test since your last visit**, if applicable.

7.3.a What was the date of the **third** test?

___ DD / ___ MO / ___ YR

7.3.b What was the result of the **third** test?

- Negative
 Positive
 Don't know

7.3.c Did you have any symptoms of COVID when you had this test?

- No
 Yes
 Don't know

7.3.d If yes, what symptoms did you have?

Only answer if Q7.3.c = YES

- Cough
 Fever
 Shortness of breath
 Sore muscles
 Headache
 Sore throat
 Diarrhea
 Decreased sense of smell or taste
 Other (specify) _____

7.4.a Have you **tested positive** for COVID-19 since your last visit on a test that wasn't included the questions above (that is, on the **4th or later test**)?

If NO, please proceed to Q8

- No
 Yes

7.4.b If yes, what was the date the first time you tested positive since your last visit?

Only answer if Q7.4.a = YES

___ DD / ___ MO ___ YR

Section 2: Exposure

8. Have you traveled outside of your home province since your last visit?

- No
 Yes
 Prefer not to answer

9.a Since your last visit, have you worked (either paid or unpaid) in an environment where you work in close proximity to other people?

If NO or Prefer not to answer, please proceed to Q10

- No
 Yes
 Prefer not to answer

9.b If yes, have you been working in any of the following occupations or worksites since your last visit? Please select all that apply.

Only answer if Q9.a = YES

- Hospital or health care facility
 First responder (paramedic/firefighter/police officer)
 Childcare worker
 Correctional officer
 Teacher or other school staff
 Transit driver
 Food service industry
 Grocery store
 Pharmacy
 Hairdresser or barber
 Aesthetician
 Flight attendant
 Factor worker
 Other (specify) _____
 Prefer not to answer

10. How many times have you been in a gathering of 10 or more since your last visit?

_____ OR Prefer not to answer

Section 3: Vaccine

11. Have you been vaccinated against COVID-19 since your last visit? Answer YES if you have **received at least one dose of the COVID-19 vaccine since your last visit.**

If NO or Prefer not to answer, proceed to the end of this questionnaire

- No
 Yes
 Prefer not to answer

12. How many doses of the COVID-19 vaccine have you received since your last visit?

Only answer if Q11 = YES

- One
 Two
 More than two

13. When did you receive the **first dose** of the COVID-19 vaccine since your last visit?

Only answer if Q11= YES

___ ___ DD / ___ ___ MM / ___ ___ ___ YR

14. Which vaccine did you receive for this **first dose** since your last visit?

Only answer if Q11= YES

- Pfizer and BioNTech mRNA vaccine
 Moderna mRNA vaccine
 AstraZeneca Oxford vaccine
 Other (specify) _____
 Janssen (Johnson & Johnson) vaccine
 Don't know
 Prefer not to answer

15. Were you pregnant when you received this **first dose** since your last visit?

If NO or N/A, proceed to Q17

- No
 Yes
 N/A

1
2
3 16. If yes, what trimester were you in when you received this **first dose** since your last visit?

4
5 [Only answer if Q15 =YES](#)

- 6
7 First
8 Second
9 Third
10

11
12
13 17. When did you receive the **second dose** of the COVID-19 vaccine since your last visit?

14
15 [Only answer if Q12 = TWO or MORE THAN TWO](#)

16
17 ____ DD / ____ MM / ____ YR
18

19
20 18. Which vaccine did you receive for this **second dose** since your last visit?

21
22 [Only answer if Q12 = TWO or MORE THAN TWO](#)

- 23
24 Pfizer and BioNTech mRNA vaccine
25 Moderna mRNA vaccine
26 AstraZeneca Oxford vaccine
27 Other (specify) _____
28 Janssen (Johnson & Johnson) vaccine
29 Don't know
30 Prefer not to answer
31
32

33
34 19. Were you pregnant when you received this **second dose** since your last visit?

35
36 [If NO or N/A, proceed to the end of this questionnaire](#)

- 37
38 No
39 Yes
40 N/A
41
42

43
44 20. If yes, what trimester were you in when you received this **second dose** since your last visit?

45
46 [Only answer if Q19 =YES](#)

- 47 First
48 Second
49 Third
50
51

52
53 **END OF QUESTIONNAIRE**
54

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-9
Objectives	3	State specific objectives, including any prespecified hypotheses	9-10
Methods			
Study design	4	Present key elements of study design early in the paper	10-11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10-15, Table 1
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	11-12
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A (No matching)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	15-17
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11 (SSO cohort-same time points and methods). 12-13, 15-16,
Bias	9	Describe any efforts to address potential sources of bias	14-15, 22-26 (limitations discussed)
Study size	10	Explain how the study size was arrived at	14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	19
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	19
		(b) Describe any methods used to examine subgroups and interactions	19

		(c) Explain how missing data were addressed	19
		(d) If applicable, explain how loss to follow-up was addressed	19
		(e) Describe any sensitivity analyses	19
Results			Protocol paper thus results not yet available
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A protocol paper results not yet available
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	22-26
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on	32

	which the present article is based	
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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

For peer review only

BMJ Open

CTN 328: Immunogenicity outcomes in people living with HIV in Canada following vaccination for COVID-19 (HIV-COV)-Protocol for an observational cohort study

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Primary Subject Heading :	HIV/AIDS
Secondary Subject Heading:	Immunology (including allergy), Infectious diseases, Patient-centred medicine
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, COVID-19, IMMUNOLOGY, VIROLOGY



PROTOCOL

CTN 328: Immunogenicity outcomes in people living with HIV in Canada following vaccination for COVID-19 (HIV-COV)-Protocol for an observational cohort study

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ABSTRACT

Introduction: Most existing vaccines require higher or additional doses or adjuvants to provide similar protection for people living with HIV (PLWH) compared to HIV-uninfected individuals. Additional research is necessary to inform COVID-19 vaccine use in PLWH.

Methods and analysis: This multi-centred observational Canadian cohort study will enroll 400 PLWH aged ≥ 16 years from Montreal, Ottawa, Toronto and Vancouver. Subpopulations of PLWH of interest will include: 1) >55 years of age 2) CD4 counts <350 cells/mm³ 3) multimorbidity (≥ 2 comorbidities) and 4) “stable” or “reference” PLWH (CD4 T cells ≥ 350 cells/mm³, suppressed viral load for ≥ 6 months and ≤ 1 comorbidity). Data for 1000 HIV-negative controls will be obtained via a parallel cohort study, (Stop the Spread Ottawa (SSO), using similar time points and methods. Participants receiving ≥ 1 COVID-19 vaccine will attend 5 visits: pre-vaccination; 1 month following the first vaccine dose; and at 3, 6 and 12 months following the second vaccine dose. The primary endpoint will be the percentage of PLWH with COVID-19-specific antibodies at 6 months following the second vaccine dose. Humoral and cell-mediated immune responses, and the interplay between T cell phenotypes and inflammatory markers, will be described. Regression techniques will be used to compare COVID-19-specific immune responses to determine whether there are differences between the “unstable” (CD4 <350) PLWH group, the stable PLWH cohort and the HIV-negative controls, adjusting for factors believed to be associated with immune response. Unadjusted analyses will reveal whether there are differences driving factors associated with group membership.

Ethics and Dissemination: Research ethics boards at all participating institutions have granted ethics approval for this study. Written informed consent will be obtained from all study participants

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3 prior to enrolment. The findings will inform the design of future COVID-19 clinical trials, dosing
4 strategies aimed to improve immune responses and guideline development for PLWH.
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8 **Trial registration:** [clinicaltrials.gov NCT04894448](https://clinicaltrials.gov/ct2/show/study/NCT04894448)
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11 **Keywords:** HIV; COVID-19; observational study; COVID-19 vaccines; vaccine immunogenicity
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19 **Strengths and Limitations of this study**

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21 • The largest and most comprehensive immunogenicity study in people living with HIV in
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• Canada receiving COVID-19 vaccination
- Emphasis on recruiting participants frequently excluded from pharmaceutical company-
sponsored trials and those most likely to have poor outcomes following COVID-19
infection (including individuals of older age, immune non-responders and persons with
multimorbidity)
- Assays used will enable differentiation between individuals with immunity from natural
COVID-19 infection vs. vaccine-induced immunity, in addition to detection of immunity
towards key variants of concern (VOCs)
- Involvement of community members from study conception to protocol development and
study implementation
- Limitations include relatively late study start, recruitment restricted to major urban centres
and variations in timing between vaccine doses amongst participants

BACKGROUND

In Canada today, an estimated 67,000 people are living with HIV (PLWH), 30% of whom are immune non-responders,¹ defined as achieving undetectable HIV viral levels without robust CD4 T cell count recovery (<350 cells/mm³). Even with fully suppressed viral load on antiretroviral therapy (ART), chronic HIV infection is characterized by a low-grade elevation in pro-inflammatory and procoagulant biomarkers linked with higher mortality²⁻⁴. Poor immunogenicity to common vaccines, including influenza⁵, pneumococcal^{6,7}, meningococcal^{6,7} and hepatitis A⁸⁻¹⁰ and B vaccines,¹¹⁻¹³ is well-documented in PLWH with low CD4 T cell counts (<200 cells/mm³) and unsuppressed viral loads¹⁴⁻¹⁶. PLWH face other intersecting vulnerabilities that increase their risk of SARS-CoV-2 acquisition and symptomatic/severe COVID-19; they commonly belong to low socioeconomic or racialized groups disproportionately affected by COVID-19 and have higher rates of risk factors for severe COVID-19 disease (e.g., multiple chronic comorbidities).¹⁷⁻¹⁹ Yet, this priority population has been understudied in COVID-19 vaccine clinical trials.^{3, 20} Most HIV seropositive participants enrolled in COVID-19 vaccine trials had normal CD4 T cell counts (>500

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4 cells/mm³) and few comorbidities.^{21,22} As such, the immunogenicity results may not represent the
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6
7 wide spectrum of PLWH who are followed in Canadian centres today.
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14 For the AstraZeneca/Oxford COVID-19 vaccine trial (ChAdOx1, n=160 PLWH) inclusion criteria
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17 specified younger age (<55 years old) and high CD4 T cell count (>350 cells/mm³) while
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20 excluding medical comorbidities (e.g., heart, kidney, liver, respiratory diseases etc.).²¹ The data
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23 obtained from PLWH were not included in the primary publication.²¹ The Moderna trial included
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26 HIV-positive participants (n=176 PLWH) with CD4 T cell count ≥ 350 cells/mm³ and an
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29 undetectable HIV viral load within the past year.²³ COVID-19 infection developed in 11 PLWH
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32 who received placebo but none who received the Moderna vaccine. The Johnson and Johnson trial
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35 (n=1218 PLWH) included participants with “stable/well-controlled HIV infection” (defined as
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38 CD4 T cell counts ≥ 300 cells/ μ L within 6 months prior to screening and documented HIV viral
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41 load <50 copies/mL within 6 months prior to screening) but excluded participants with ongoing
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44 and progressive comorbidities associated with HIV infection.²⁴ COVID-19 infection developed in
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48 2 vaccinated PLWH and 4 PLWH given placebo. The Novavax trial, conducted in South Africa,
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54 excluded PLWH with chronic cardiovascular disease, gastrointestinal disease, liver disease, renal
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3 disease, endocrine disorder and neurological illness, as well as participants with very high body
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6 mass index (≥ 40 Kg/m²).²² As reported by Vivek *et al.* (2021), efficacy of the NVX-CoV2373
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10 COVID-19 vaccine against the B.1.351 variant was examined in 1,857 individuals in South Africa,
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13 of whom 30% (500 individuals) had HIV infection²⁵. The vaccine efficacy estimate in baseline
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16 seronegative HIV-negative participants was 52.2% (95% confidence interval: -24.8 to 81.7).
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19 During the first 60 days of follow-up, the incidence of Covid-19 in HIV-negative placebo
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22 participants (5.3% [95% CI: 4.3 to 6.6]) was comparable to the incidence in PLWH placebo
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25 participants with HIV (5.2% [95% CI: 3.6 to 7.2])²⁶. Among HIV-negative participants, there were
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28 four and two cases of symptomatic Covid-19 among NVX-CoV2373 and placebo recipients,
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31 respectively (N<109 in each group)²⁶. No cases were observed in the baseline HIV-positive
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34 population (N<33 in each group)²⁶. Among 94% of participants without HIV, vaccine efficacy was
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37 60.1%. The study was not powered to detect efficacy in the small population of PLWH²⁶.
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41 While several other trials included PLWH, they excluded their data from primary
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44 publication^{20,21,27}. In a recent report by Ruddy *et al.*(2021) which examined COVID-19 antibody
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47 response in 12 PLWH with a median of 21 days (interquartile range 17-27) following the first dose
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50 of mRNA vaccine (50% Moderna and 50% Pfizer), antibodies were detected in all participants
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53 although lower levels were observed in persons with lower CD4 T cell counts²⁶. In this study, all
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4 12 individuals were male, 8% were non-white, all had been on ART \geq 6 months and 92% had an
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7 undetectable HIV viral load. Two individuals had a CD4 T cell count below 200 cell/mm³.²⁶
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10 We lack robust data on vaccine immunogenicity and immune response durability in
11
12 subpopulations of PLWH. No evidence is available on the durability of immunogenicity in PLWH
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14 beyond 3 months following vaccination. Since the hallmark of HIV infection is a reduced number
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16 and function of CD4 T cells, and cell-mediated immunity has emerged as a critical aspect of the
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18 COVID-19 immune response,^{28,29,30} it is critical to characterize cellular immune and cytotoxic T
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20 cell responses to COVID-19 vaccination.³¹⁻³³
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28 Given that inflammatory markers may influence immune cell activation status and shift cell
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30 profiles towards either Th1 or Th2 responses, impacting vaccine-elicited immune response³⁴,
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32 understanding the interplay between immune activation and dysfunction is also important. To
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34 address this need, we are establishing a pan-Canadian prospective cohort of PLWH receiving
35
36 COVID-19 vaccines to assess humoral and cellular immunogenicity and to describe the
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38 inflammatory milieu in this context. Safety and tolerability of COVID-19 vaccines in this cohort
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40 of PLWH will also be captured. Of note, COVID-19 vaccines currently approved for use in
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42 Canada include those manufactured by Pfizer, Moderna, AstraZeneca and Janssen (Johnston &
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44 Johnston) ([https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-](https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/list-drugs.html)
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46 industry/drugs-vaccines-treatments/authorization/list-drugs.html). Since the beginning of the
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48 vaccine roll-out Pfizer and Moderna vaccines were administered most often as they were the first
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3 to gain approval by Health Canada. Although approved, due to concerns associated with cerebral
4 venous sinus thrombosis and vaccine-induced immune thrombotic thrombocytopenia, use of the
5 AstraZeneca COVID-19 vaccine has been restricted in some provinces.
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11 12 13 **Study Objectives:**

14 15 16 Primary objective:

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18 To evaluate the immunogenicity of COVID-19 vaccination in PLWH, by specific immunoglobulin
19 G antibody enzyme-linked immunosorbent assay (ELISA), at 6 months following 2nd vaccine dose.
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23 24 Secondary objectives:

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27 1) To assess neutralization capacity of COVID-19-specific IgG at 6 months following 2nd vaccine
28 dose.
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32 2) To assess the durability of COVID-19-specific IgG response in PLWH at 12 months following
33 vaccination.
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37 3) To examine changes in the proportion and activation phenotype of CD4 T cells, CD8 T cells, B
38 cells, natural killer cells and monocytes, including gene expression and cytokine production, pre-
39 and post-COVID-19 vaccination at 6 months following 2nd vaccine dose.
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45 4) To determine safety and tolerability of COVID-19 vaccines in PLWH, based on local or
46 systemic adverse events following first or second injections.
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49 50 Exploratory objectives:

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52 1) To determine if subpopulations of PLWH respond differently to COVID-19 vaccination.
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54 Subpopulations of interest include, 1) PLWH >55 years of age; 2) immune non-responders (ART
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3 treated, and fully suppressed HIV RNA (<40 copies/mL), but CD4 T cell counts below 350
4 cells/mm³ and CD4/CD8 T cell ratio <0.75); 3) PLWH with multimorbidity (2 or more chronic
5 diseases) and 4) PLWH “reference” participants (with CD4 T cells >350 cells/mm³, suppressed
6 viral load for at least 6 months, and have at most 1 comorbidity) (*Note: groups will not be mutually*
7 *exclusive but will likely have overlapping characteristics*)
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12 (2) To investigate if current COVID-19 vaccines elicit IgG that cross-recognize key COVID-19
13 variants of concern (VoC), and if this differs in PLWH compared to individuals without HIV
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16 (3) To compare virus-specific T cell responses generated by COVID-19 vaccines in PLWH and
17 compare results with HIV-negative populations
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28 **METHODS AND ANALYSIS**

29 **Study design**

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31 This study is a multi-centre prospective observational cohort study. Approximately four hundred
32 (400) PLWH aged ≥ 16 years will be recruited from 4 sites in 3 Canadian provinces including 1)
33 McGill University Health Centre/Jewish General Hospital (Montreal), 2) Ottawa Hospital
34 Research Institute, 3) The University Health Network (Toronto), and 4) St. Paul’s Hospital
35 (Vancouver). These sites were selected since they are 4 of the largest HIV clinics in Canada and
36 have established research infrastructures to support the recruitment, enrolment and follow-up of a
37 high volume of diverse study participants. These sites also have strong track records for rapid
38 enrollment of participants in CTN studies. Many sites provide HIV care for many clients who are
39 visible minorities and multiple morbidities. This will enable our sites to recruit a study population
40 representative of PLWH most likely to be impacted by detrimental COVID-19-related outcomes.¹⁹
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3 Data for HIV-negative individuals will be obtained from the Stop the Spread Ottawa (SSO) cohort.
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5 Since we will not perform additional analyses on the samples of the SSO cohort then we can
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7 include all the participants in the SSO study and matching of HIV-negative and positive
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9 participants will not be required.
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16 Determination of which vaccine is administered at any point in time and to which individuals is
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18 dictated by Canada's provincial governments, with input from the National Advisory Committee
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20 on Immunization (NACI), and is not influenced by study investigators or staff. We will include
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22 participants irrespective of the specific type of COVID-19 vaccine. Furthermore, the duration of
23
24 the interval between 1st and 2nd doses time from when the vaccine was administered will not
25
26 influence eligibility, since Canada has decided to extend dose intervals for all 2 dose vaccines to
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28 4 months. However, the duration of interval between vaccine doses will be included as an outcome
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30 variable.
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39 **Methods: Participants, intervention and comparator and outcomes**

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41 **Inclusion Criteria:** 1) Age ≥ 16 years; 2) HIV-positive for HIV group, immunocompetent and
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43 generally in good health for the HIV-negative group; and 3) Receiving ≥ 1 dose of COVID-19
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45 vaccine. Persons are still eligible to participate if they have already received one or two vaccine
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47 doses.
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51 **Exclusion Criteria:** 1) Receipt of any blood product or immunoglobulin preparation within 1
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53 month of vaccine administration and until study completion; 2) signs/symptoms of active COVID-
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55 19 at the time of enrollment; 3) for the HIV-negative group: immunocompromised state or on
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3 immunosuppressant medications. Prior receipt of other vaccines ≤ 12 months or past COVID-19
4 infection are not exclusion criteria but will be recorded. Detectable HIV viral load on ART is not
5 exclusionary.
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10 The following groups of PLWH will be prioritized for study enrolment:

- 13 1. Older age (55 years and above). Older age is associated with immunosenescence and
14 results in lower vaccine efficacy.³⁵⁻³⁷ We have selected 55 as the specific age cut-off
15 since PLWH tend to develop comorbidities at an earlier age.
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- 18 2. Immune non-responders (CD4 T cell count < 350 cells/mm³, CD4/CD8 < 0.75 with
19 undetectable viral load for 1+ year). Immune non-responders may be at risk of more
20 adverse COVID-19 related outcomes than HIV immune responders^{38,39,40,41}.
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- 23 3. Multi-morbidity (defined as having ≥ 2 comorbidities). Comorbidities may include
24 cardiovascular disease (CVD), co-infection, hypertension, dyslipidemia, diabetes,
25 chronic obstructive pulmonary disease and obesity among PLWH^{2,42-45} and factors that
26 contribute to worse outcomes with COVID-19.⁴⁶
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- 29 4. HIV-positive “stable” or “reference” group. These persons will have undetectable HIV
30 viral load for > 6 months, CD4 T cell counts > 350 cells/mm³, and a maximum of 1
31 comorbidity. To capture the full spectrum of individuals in the HIV-negative group, we
32 will include this HIV-positive “stable” group so that we can determine whether there are
33 particular characteristics within PLWH which impact on immune response. In comparing
34 the stable and unstable groups, we will be able to determine whether participants with low
35 CD4 counts (< 350 cells/mm³) differ in their response to vaccine from those with normal
36 CD4 T cell counts while controlling for other characteristics. We aim to enroll HIV-
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3 negative and HIV-positive “stable” individuals with overlapping characteristics (i.e., some
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5 should have multiple comorbidities) so that the groups are comparable.
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9 **General Methodology and participant timeline**

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12 Participants will attend 5 visits over 12 months: pre-vaccination; 1 month following first vaccine
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14 dose; and at 3, 6 and 12 months following the second vaccine dose (**Table 1**). Each visit will last
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16 between 20-60 minutes.
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20 **Primary Endpoint:** Percentage of PLWH with COVID-19-specific antibodies at 6 months
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22 following 2nd vaccine dose.
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25 **Secondary Endpoints:** Percentage of individuals with 1) COVID-19 neutralization capacity at 6
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27 months following 2nd vaccine dose and 2) COVID-19-specific antibodies at 12 months following
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29 2nd vaccine dose. 3) Proportion and activation status of CD4 T cells, CD8 T cells, B cells, natural
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31 killer cells and monocytes, pre-vaccination and 6 months post 2nd vaccine dose.
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34 **Exploratory Endpoints:** 1) COVID-19-specific antibodies at 6 months following 2nd vaccine dose,
35
36 stratified by subpopulations. Critically, we will also assess the ability of vaccine-elicited antibodies
37
38 to cross-recognize SARS-CoV-2 S-protein variants, including N501Y and/or E484K, using in-
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40 house assays.
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47 **Sample size**

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50 Our primary outcome is the proportion of individuals in each group who mount a satisfactory
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52 immune response, although the best marker of what constitutes a satisfactory immune response is
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54 unclear at the moment and the science is rapidly evolving. We initially defined a successful
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3 immune response as a 4-fold relative rise in IgG production at 6 months.⁴⁷ We anticipated that
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5 90% of HIV-negative individuals would mount an adequate IgG response at this timepoint^{27,34},
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7 versus 70% of PLWH.^{12,48} If 20% of the sample were to have the characteristic of interest or
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9 predictor variable (e.g., 20% with multimorbidities), enrolling 200 PLWH and 50 HIV-negative
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11 participants would provide sufficient statistical power (>80%) to detect a 20% difference in
12
13 outcomes between groups whatever the exact proportions. This sample size was determined using
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15 the UCSF sample size calculator (<https://data.ucsf.edu/research/sample-size>) which uses the
16
17 typical normal distribution assumption with the continuity correction as an approximation to the
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19 binomial distribution. In addition, we calculated that we would have >80% power to detect a 20%
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21 difference in outcome between those with suppressed CD4 count or unsuppressed viral load and
22
23 the HIV- group. Previous studies of temporal differences in humoral and cellular responses to
24
25 COVID-19 have shown differences between individuals when sample sizes included 100
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27 participants or fewer.⁴⁹⁻⁵³ We would also have >80% power to detect a 20% difference in outcome
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29 between the higher risk PLWH (ie, with CD4 counts <200 cells/mm³ and/or unsuppressed HIV
30
31 viral load) and the HIV-negative group. Such recruitment targets would also also provide a
32
33 sufficient buffer to account for potential drop-outs of 5-10%. However, to increase our ability to
34
35 detect differences in our primary outcome between the four sub-populations of interest (individuals
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37 of older age; immune non-responders; persons with multimorbidity; and an HIV-positive “stable”
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39 or “reference” group), we plan to recruit 400 PLWH and use data from the *entire* cohort of HIV-
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41 negative individuals in the SSO study (approximately 1000 individuals) to increase power.
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43 Inevitably, the higher risk groups will be overlapping, so we will recruit a minimum of 20% of the
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45 400 PLWH per category. By using the entire cohort of HIV-negative individuals in the SSO study,
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47 we avoid the need to match PLWH and HIV-negative participants.
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Recruitment

Participants will be informed about the study through a recruitment flyer during routine physician visits to their HIV clinic and via established recruitment strategies through our community partners and the CIHR Canadian HIV Trials Network (CTN) via webpages, email, and social media platforms. Individuals followed for routine HIV care at clinics other than the 4 enrolment sites are eligible to participate if they can come to the enrolment site for study visits. Participants will be compensated \$40 per study visit to help offset the time commitment and parking fees. We will make a concerted effort, through the use of recruitment quotas, to ensure the HIV-negative and HIV-positive “stable” groups have overlapping characteristics (eg, age >55 years, CD4 count <350 cells/mm³, comorbidities) so that the groups will be comparable.

Data Collection

Medical history and HIV history will be gathered from both patient interviews and clinic chart reviews following written informed consent. Information extracted will include comorbidities, year of HIV diagnosis, CD4 T cell nadir (if known) in addition to tobacco smoking and cannabis use history. Medications will be recorded in addition to the ART regimen. History of COVID-19 infection and date of confirmatory test will be recorded.

Sample Collection: At each visit, blood will be collected to isolate serum, plasma and peripheral blood mononuclear cells (PBMCs).

Humoral Immunity (SARS-CoV-2 Binding Antibodies): We will evaluate levels of immunoglobulins M and A (IgM, IgA) and IgG targeting the SARS-CoV-2 Spike (S) protein

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3 receptor-binding domain (RBD) and nucleocapsid protein using a high-throughput automated
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5 ELISA co-developed and validated by Dr Marc-Andre Langlois,⁵⁴ thereby distinguishing vaccine-
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7 induced (S only) from infection-induced (S and nucleocapsid (N)) responses. We will also evaluate
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9 samples for IgM and IgG antibody cross-recognition of RBD derived from VoCs, including those
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11 harbouring *N501Y* and/or *E484K* (e.g., Alpha and Beta strains, respectively) using a commercial
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13 multiplex ELISA (V-Plex, Meso Scale Discovery). This assay is updated regularly by the
14
15 manufacturer to accommodate emerging spike variants. We will test plasma samples for their
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17 capacity to block viral entry using a well-established neutralization assay based on retroviruses
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19 pseudotyped with the SARS-CoV-2 S protein.^{49,51}
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24 **Cellular Immunity:** Flow cytometry will be performed to enumerate CD4 T cells (including helper
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26 and regulatory subsets), CD8 T cells and other T cell subsets (including naïve, central memory,
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28 transitional memory, effector memory and terminally differentiated cells), B cells (including naïve,
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30 memory and antibody-secreting B cells), Natural Killer cells and monocytes (classical,
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32 inflammatory and non-classical). We will also evaluate markers of cellular immune activation,
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34 senescence and exhaustion. Following high-resolution Human Leukocyte Antigen class I/II typing,
35
36 we will examine COVID-19-specific T cell responses using an activation-induced marker (AIM)
37
38 assay. Briefly, PBMCs will be stimulated overnight with pools of SARS-CoV-2 S peptides.
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40 Activated CD4 and CD8 T cells will be quantified by flow cytometry-based expression of CD137,
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42 OX40 and/or CD69. Gene expression will be assessed by single-cell RNA sequencing of PBMC
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44 as described previously.⁵⁵ T and B cell epitope specificity will be confirmed using virus-derived
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46 antigens (peptide/HLA or RBD dextramers, respectively). Plasma levels of inflammatory markers
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48 including interferon (IFN)- γ , interleukin (IL)-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, IL-17,
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50 transforming growth factor (TGF)- β , IFN- γ -induced protein-10 (IP-10), IL-12p70 and tumour
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3 necrosis factor (TNF)- α will be measured using multiplex Luminex assays, D-dimer, C-reactive
4 protein, and markers of microbial translocation lipopolysaccharide (LPS), beta-d-glucan (β dG) and
5 soluble CD14 will be evaluated by ELISA.⁵⁶
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11 12 13 14 15 16 **Exploratory Safety and Tolerability of COVID-19 Vaccines in PLWH**

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18 In the prospective cohort, we will explore vaccine safety and efficacy to inform subsequent studies.
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20 Reactogenicity: **Symptoms Diary:** Participants will be asked to document specific local and
21 systemic reactions in a diary for 1 week and 1 month following each injection, as was done in
22 Pfizer-BioNTech Phase 3 studies.⁴⁷ We will report the proportion of participants developing local
23 (redness, pain or swelling at the injection site) or systemic effects (fatigue, headache, muscle pain,
24 fever, joint pain, diarrhea) within 7-30 days following each vaccine dose with 95% confidence
25 intervals (Supplementary information).
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35 **COVID-19 Questionnaires:** We will administer the COVID-19 System Questionnaire to
36 participants who develop a flu-like illness to confirm the illness, along with PCR-based tests for
37 COVID-19. Participants will complete the COVID-19 Immunity Task Force (CITF) Standardized
38 Core Survey Data Elements questionnaire prior to vaccination and a modified CITF questionnaire
39 (minus the demographic information) at follow-up visits (Supplementary information).
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47 If participants develop COVID-19 symptoms 14 days+ after vaccination, we will also collect CITF
48 system questionnaire (length of illness and symptomatology, which vaccine was administered,
49 number of vaccine doses received) and saliva specimens to enable study of COVID-19 variants of
50 concern. ([https://www.covid19immunitytaskforce.ca/covid-19-immunity-task-force-releases-
51 standardized-core-survey-data-elements/](https://www.covid19immunitytaskforce.ca/covid-19-immunity-task-force-releases-standardized-core-survey-data-elements/))
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Data management

The study sponsor, the CTN, will be responsible for national project management, database development, data management and data analysis. To facilitate data sharing, we will: 1) use standard encodings for CITF-defined Core Data Elements; 1) request immunogenicity study participants consent to data sharing as guided by the CITF, including collecting survey elements and saliva 14+ days after vaccination on symptomatic participants to determine whether the infecting strain is a COVID-19 VoC and 3) rapidly share interim data and all requested study metadata for cataloguing.

Confidentiality

All participant-related information, including Case Report Forms, laboratory specimens, evaluation forms and reports, will be kept strictly confidential. All records will be held in a secure, locked location and only accessible to research staff. Participants will be identified using a coded number specific to each participant. All computerized databases will identify participants by numeric codes only and will be password protected. Upon request, and in the presence of the investigator or his/her representative, participant data will be made available to the study sponsor, monitoring groups representative of the study sponsor, representatives of funding groups, and applicable regulatory agencies to verify clinical study procedures and/or data, as permissible by local regulations.

Statistical Analyses

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3 We will use regression techniques to compare COVID-19-specific immune responses applying
4 data transformation where necessary to conform with distributional assumptions in order to
5 determine whether there are differences between the “unstable” (CD4<350) PLWH group, the
6 stable PLWH cohort and the HIV- controls, taking into account factors that are believed to be
7 associated with immune response. We will also perform unadjusted analyses to determine
8 whether there are differences which may or not be driven by factors associated with group
9 membership. We will report data from exploratory analyses with descriptive statistics and data
10 for vaccines from different manufacturers separately and combined. We will stratify results by
11 the number of doses received and the time interval between the two doses in case these factors
12 drive response and differ between groups. We will stratify immunogenicity data by sex as
13 females and males have differences in both vaccine-elicited immune responses⁵⁷ and adverse
14 effects from vaccines.⁵⁸ Furthermore, we will stratify analyses by individuals who are naive
15 to COVID-19 versus those with pre-existing antibodies as a result of prior COVID-19
16 infection. This will be important since antibody responses (particularly after the 1st dose) will
17 be much higher in convalescent individuals,^{59,60} so it is not appropriate to include them with
18 individuals who do not have pre-existing antibodies to COVID-19.
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46 **ETHICS AND DISSEMINATION**

47 **Ethics approval and consent to participate**

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51 Written informed consent will be obtained from all study participants. The study will be conducted
52 in accordance with the Declaration of Helsinki. At the time of initial manuscript submission (June
53 2021), a very closely related protocol had been approved by the University of British
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3 Columbia/Providence Health Care Research Institute and Simon Fraser University Research
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5 Ethics Boards. The present protocol was later approved by the Research Institute of the McGill
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7 University Health Centre (2nd review), the Ottawa Hospital Research Ethics Board, the University
8
9 of Toronto Research Ethics Board. Patient enrollment for this trial began June 2021. Both the
10
11 protocol and informed forms were reviewed and approved by the CTN Community Advisory
12
13 Committee.
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20 **Availability of data and materials**

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23 De-identified participant data will be stored on a secure password-protected RedCap database.
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25 Access to the database will be controlled by the CTN. Access to the final study database will be
26
27 provided upon written reasonable request to the corresponding author/principal investigator
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29 following publication and CTN and CITF approval.
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34 We will standardize reagents and analysis strategies, where possible, working with the Immune
35
36 Sciences Network and Testing Working Party recommendations to enable data sharing and avoid
37
38 duplication in consultation with other CIHR and CITF-funded vaccine surveillance projects. We
39
40 will also contribute results to SeroTracker, a knowledge hub that tracks and synthesizes findings
41
42 from SARS- CoV-2 serosurveillance efforts worldwide
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44 (<https://www.covid19immunitytaskforce.ca/serotracker/>). To inform COVID-19 immunization
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49 guidelines and future interventions for PLWH in Canada and internationally, we are committed to
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53 sharing results with all stakeholders and will adhere to Wellcome's *Sharing research data and*
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4 *findings relevant to the novel coronavirus (COVID-19) outbreak* statement.⁶¹ Data sharing
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6 agreements will be obtained between CTN sites to use data not sent to the CITF.
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15 **Knowledge Translation (KT) & Dissemination Plan**

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18 Serology results will be provided to individual study participants at the end of the study, along
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20
21 with a summary of study results and their implication in lay language. We prioritize meaningful
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24 community engagement and our Community Advisory Committee includes PLWH and
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27 representation from the Canadian Aboriginal AIDS Network. The Community Advisory
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4 completing the 6-month post 2nd vaccine dose study visit. A second manuscript outlining the
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7 durability results will be submitted for publication within 6 months of participants completing the
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10 12-month post 2nd dose study visit. Data will also be shared with CTN members at the semiannual
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13 meetings and through conference abstracts.
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23 **Patient and Public Involvement**

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26 The CTN Community Advisory Committee (CAC) was involved in the peer review process of this
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28 study proposal and deemed that the research questions addressed were of very high priority to
29
30 PLWH. The CAC's critiques of the initial proposal were taken into account in the revised
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32 proposal. Two members of the CAC (SM and EM) were involved in finalizing the study design,
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34 inclusion/exclusion criteria, outcome measures and monitoring plans and are formal study
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36 investigators and co-authors. Community consultants will receive financial compensation to
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38 recognize their time commitment and expertise.
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45 **DISCUSSION**

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48 Herein, we present the protocol for an observational cohort study to evaluate COVID-19 vaccine-
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50 elicited immunogenicity in PLWH, with a priority of determining immunogenicity in PLWH who
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52 are of older age, immune non-responders and those with multimorbidity. These 3 groups were
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3 selected since they represent subpopulations most likely to experience poor outcomes following
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5 COVID-19 infection and have a weaker immune response to vaccination.
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11 PLWH immune non-responders are at risk of more adverse COVID-19 related outcomes than HIV
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13 immune responders. In the study performed by Braunstein *et al.* (2021), PLWH with COVID-19
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15 had a higher proportion of hospital admissions, intensive care unit (ICU) admission and death.
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17 Those who experienced these COVID-19-related outcomes had CD4 T cell counts below 500
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19 cells/mm³.^{3,38} Similarly, the study by Dandachi *et al.* (2021) found that having CD4 T cell counts
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21 below 200 cells/mm³ was associated with severe outcomes such as ICU admission, intubation and
22
23 death.³⁹ Furthermore, a multicentre cohort study by Hoffman *et al.* showed that CD4 T cell counts
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25 <350 cells/mm³ were associated with severe COVID-19 (adjusted OR 2.85, 95% CI 1.26-6.44).⁴⁰
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28 However, in a group of patients with inborn errors of immunity, Kinoshita *et al.*(2021) they
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30 demonstrated robust T cell activity and humoral immunity against COVID-19 structural proteins
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32 in some patients with antibody deficiency,⁶² underscoring the heterogeneity and complexity of
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34 immune response.
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42 A major challenge with planning this study is the unprecedented, rapidly-changing nature of the
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44 COVID-19 pandemic and evolving scientific information. As a result, data on the optimal time
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46 points to assess immune responses post COVID-19 vaccination administration are rapidly
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48 changing, resulting in multiple adjustments in our protocol plans. Within Canada, the vaccination
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50 schedule is determined by provincial vaccination programs based on review of evidence,
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52 population risk factors and local infection rates, along with input from NACI. However,
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54 differences exist between provinces regarding to vaccine supply, eligibility criteria, type of vaccine
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3 administered and time period between vaccine doses. We are mitigating these challenges by
4 holding monthly meetings with teams to discuss these issues over the previous month, troubleshoot
5 and adjust recruitment priorities accordingly for the upcoming months. Ideally, and under non-
6 pandemic circumstances, we would establish, a priori, methods for analyzing data from single vs.
7 two-dose vaccines. However, in the current context with uncertainty of vaccine supply and
8 distribution, such detailed plans are impractical and will depend on the methods of vaccination
9 used in the participants enrolling in this study. This statement holds true for other variables we
10 will likely encounter, such as different dosing intervals amongst persons receiving two-dose
11 vaccines.
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29 The importance of advanced age in impaired vaccine-induced immunogenicity is well-
30 documented. Due to a combination of disrupted posttranscriptional regulation, T cell receptor
31 signalling, and metabolic function, older individuals demonstrate reduced quantity and
32 functionality of T-cells^{63,64}. When this balance is disrupted, T-cells exhibit shorter-lived effector
33 phenotypes rather than memory or follicular helper T cells and vaccine-induced antibodies are less
34 protective than in younger persons^{63,64}. As the elderly are considered a priority vaccination group,
35 many of them were eligible for vaccination in early 2021 in Canada, before this current study
36 began, meaning that baseline plasma, serum and PBMCs will not be available for participants in
37 this subpopulation of interest. Another drawback with starting this study in May 2021 is that we
38 may miss other important groups of PLWH, including Indigenous persons, who were prioritized
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3 as high-risk populations for immunization and were eligible to receive COVID-19 vaccines at a
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5 younger age than the general population.
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12 Another major challenge with the planning of this study was the need to ensure an adequate sample
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14 size to meet the primary objective in the group as a whole, but also in important subpopulations of
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16 PLWH. Enrollment of such a large number of individuals, with follow-up until 12 months
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18 following the second vaccine dose, is very resource-intensive and requires dedicated study
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20 participants. We will provide individualized antibody results to participants at study completion to
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22 increase study engagement and prevent drop-outs. Furthermore, due to the need to rapidly enroll
23
24 participants to match the pace of the COVID-19 vaccine rollout, we decided to use CTN study
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26 sites with large clinic volumes and proven capacity to recruit. However, these clinics are based in
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28 urban centres and, therefore, may follow individuals who differ systematically from PLWH who
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30 live in rural areas. PLWH who live in cities may be of higher socioeconomic status and consist of
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32 more men who have sex with men (MSM). Therefore, each site will need to make a concerted
33
34 effort to recruit sufficient participants with other profiles. For this reason, we will employ a flexible
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36 recruitment strategy, whereby sites that can recruit the required participants with characteristics of
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38 interest more easily than other sites can help to make up for lower recruitment flexibility at other
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40 sites. As with many studies, recruitment of women living with HIV may be challenging. Due to
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42 our connection with other studies within the CTN and the help of our community advisory board,
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44 we are encouraging clinics with predominantly female clients to ensure they inform their female
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46 patients living with HIV about this study.
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3 Currently, the immune correlate of protection against COVID-19 is undefined. T cell and B cell
4 responses are usually used as surrogates of protection.⁶⁵ We decided to use a 4-fold rise from
5 baseline in IgG production following second vaccine dose as the criteria for a successful vaccine
6 response, as was indicated in the Pfizer study⁴⁷. Data from the Pfizer study submitted to the Food
7 and Drug Administration and published by Walsh *et al.*, report geometric mean titers that were
8 compared to those from a human SARS-CoV-2 convalescent serum panel as a benchmark.
9 Increased titers were expressed in logarithmic fold increases.⁶⁶ There are currently no national
10 standards for presenting the serology data. Some groups prefer to report the raw signal values,
11 whereas others normalize data as fold increases. Since individual baseline values will not be
12 available for participants who have already received their first vaccine dose, one option is to use
13 the cohort baseline data derived from non-vaccinated participants. Alternatively, we may opt to
14 examine relative titers, or fold-changes, and therefore baseline data will not actually be required.
15 Since science is continuously evolving, we will use the definition of a successful vaccine response
16 which is most widely accepted at the time of publication.
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39 The best methodology to match PLWH with the HIV-negative group remains unclear, and there is
40 no optimal approach to match participants to controls. As discussed by Wong *et al.* (2014), the
41 ideal comparison group would be individuals who are identical to HIV-negative adults in all
42 aspects except HIV status⁶⁷. As PLWH have distinct characteristics, traditional risk factors,
43 lifestyle factors and socioeconomic factors compared to the general population, the general
44 population may not be the ideal comparison group⁶⁷. Differences include increased tobacco
45 smoking⁶⁸, substance use⁶⁹ and comorbidities⁷⁰ amongst PLWH compared to the general
46 population. However, PLWH also undergo more screening for age-related comorbidities due to
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3 frequent contact with health care providers⁶⁷. Since matching is challenging, we will avoid the
4 need to match individuals entirely, by using a large existing dataset of over 1000 individuals
5 without HIV infection. As previously mentioned, as long as we ensure there are 20% of individuals
6 with the characteristics of interest in the HIV-negative and HIV-positive “stable” cohorts, we can
7 compare groups while adjusting for these characteristics via regression.
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15 The findings from this study will provide valuable insight into COVID-19-vaccine-induced
16 immunogenicity in important sub-populations of PLWH. HIV-positive persons of older age, with
17 CD4 counts <350 cells/mm³ and multimorbidity were not included in the early clinical trials, yet
18 are most likely to suffer from poor outcomes if infected with COVID-19. These findings will
19 inform clinical guidelines and recommendations for PLWH and, in turn, reduce COVID-19-
20 induced morbidity and mortality.
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Authors' contributions

Co-principal investigators of the study are CTC, CLC and AHA. CTC and CLC conceived the study, led the proposal and protocol development. CTC wrote the first draft of the manuscript. JS is the biostatistician who provided methodological expertise and performed sample size

1
2
3 calculations. All other authors, including ANB, JN, IK, SM, EM, MAO, CMK, DHST, SLW, MH,
4
5 MWH and JBA contributed to protocol development, study design and development of the
6
7 proposal. CTC, MAL, MAJ, MAO, MAB, and ZLB designed the laboratory evaluations. MAL
8
9 will be responsible for studies on humoral immunity. MAJ will be responsible for flow cytometric
10
11 studies to define proportions of immune cells and their subsets, while CTC will be responsible for
12
13 cytokine assessment. MAB and ZLB will be responsible for RNA profiling. MAL and MAB will
14
15 perform the analysis of antibodies to COVID-19 variants. MAO and MAB will perform analyses
16
17 of T cell responses to vaccine immunogens. Markers of gut barrier damage, microbial
18
19 translocation and CMV IgG titers will be performed by JPR. HLA typing will be performed as
20
21 necessary for participants evaluated for T cell responses by MAO, ZLB and MAB. JS will oversee
22
23 data analysis between groups and subgroup analyses. All authors critically reviewed and approved
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24 **Competing interests**

25
26 The authors declare that they have no competing interests
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Table 1: Visits and Procedure Schedule

Visit number	1 ¹ (Screen)	Vaccine	2	Vaccine	3 ⁶	4 ⁶	5 ⁶
Week Number	-12 to 0 weeks	0	4 weeks		3 mo after dose 2	6 mo after dose 2	12 mo after dose 2
Window	-3 mo						
Inclusion/Exclusion	X		X				
Informed Consent	X						
Medical History	X						
Blood: Immunology ²	X		X		X	X	X
Blood Draw: CD4/Viral Load ³	X		X		X	X	X
Vaccination ⁴		X		X			
Participant Diary ⁵		X	X	X	X		
CITF ⁷ Questionnaire	X		X		X	X	X
Adverse Events ⁸			X		X		
Concomitant Meds	X		X		X	X	X

1
2
3 ¹Screening assessment may be performed same day as vaccination but will be completed
4 prior to vaccination.

5
6
7
8 ²Immunoglobulin levels flow cytometry and cytokine secretion (immunogenicity
9
10 measures); Will be collected at each visit. For participants who have already received a
11
12 vaccine dose prior to study enrolment, “baseline” immunoglobulin levels (i.e., pre-
13
14 vaccination) may not be available.

15
16
17 ³Blood work such as CD4 and Viral load can be collected as part of standard of care

18
19 ⁴Participants will receive the COVID-19 vaccine outside of the study per standard of care
20
21 as part of their provincial immunization program.

22
23
24 ⁵Participants will be given a printed diary after vaccination during which they will record
25
26 their vaccine reactions, oral temperature and any febrile respiratory tract symptoms as
27
28 well as general changes to health and medications. The diary will be evaluated up to 30
29
30 days following each injection.

31
32
33 ⁶Visits 3, 4, 5 will be conducted at 3, 6, 12 months after dose 1 respectively, for COVID-
34
35 19 vaccines administered as a one-dose schedule.

36
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38 ⁷The full CITF questionnaire will be completed at visit 1 and the modified CITF
39
40 questionnaire will be completed at subsequent visits.

41
42 ⁸Adverse events will only be collected at 7 and 30 days post vaccination and for
43
44 participants who receive a vaccine while currently enrolled in the study (i.e. adverse
45
46 events will not be collected retrospectively)

47
48
49 For participants who develop COVID19-symptoms 14+ days following vaccination.

50
51 Participants will be asked to complete the COVID-19 Symptom Survey (Supplementary
52
53 materials) and to go for a COVID-19 test at their nearest test centre and notify the study
54
55

1
2
3 staff of their test result. If positive for COVID-19, the study staff will mail the participant
4
5 6 saliva collection kits by courier in order to collect information on SARS-CoV-2
6
7
8 variants
9

10 Participants who have already received 1 vaccine dose: These individuals may be
11
12 enrolled in the study at any duration of time post first dose as long as the baseline blood
13
14 drawn is before the second booster. Visits 1 and 2 will be combined.
15
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19 Participants who have already received 2 vaccine doses: These individuals must be
20
21 enrolled in the study within 3 months of their 2nd dose. Visits 1 and 3 will be combined
22
23 and Visit 2 will not be required. Participants will follow-up at visits 4 and 5.
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CTN 328
HIV-COV

DATA COLLECTION
WORKSHEET

Participant ID

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Vaccine 1

Vaccine 2

COVID-19 SYMPTOMS QUESTIONNAIRE

Have you experienced any of the following COVID-19 signs or symptoms?

Sign	Yes	No	If yes, provide date, time
Fever, chills			
Cough			
Shortness of breath			
Acute loss of smell or taste			
Fatigue			
Headache			
Muscle aches			
Nausea/Vomiting/Diarrhea			
General weakness			
Nasal congestion			
Sore throat			



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DATA COLLECTION
WORKSHEET

Participant ID

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Vaccine 1

Vaccine 2

PARTICIPANT DIARY

Following each injection of COVID-19 vaccine, please indicate whether you experienced any of the following, within 7 days and within 30 days, and indicate the severity. See the Other Signs or Symptoms worksheet for a guide to the severity levels.

	Date:	Date:	Date:	Date:	Date:	Date:	Date:	Date:	
Sign or Symptom	Day 0*	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Within 30 days
Pain at injection site									
Redness									
Swelling									
Lymphadenopathy/Axillary swelling and tenderness									
Fatigue									
Headache									
Muscle Pain									
Chills									
Joint pain									
Fever									
Diarrhea									
Nausea and/or Vomiting									

* Day 0 refers to day vaccine received, Day 1 is the *following day*, and so forth

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Initials: _____

Date: _____

Page ____ of ____



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CTN 328: HIV-COV

CITF CDE BASELINE QUESTIONNAIRE

This version is only administered at Screening

Please answer all questions unless otherwise indicated

Participant ID: _____

Section 1: Demographics

1. Date (DD-MMM-YYYY):

____ / ____ / _____

2. What is your age?

_____ YRS _____ MO OR Prefer not to answer

3. What was your assigned sex at birth?

- Male
- Female
- Prefer to self-describe (specify) _____
- Prefer not to answer

4. What is your sex now?

- Male
- Female
- Prefer to self-describe (specify) _____
- Prefer not to answer

1
2
3 5. What is your gender (how do you currently self-identify)?
4

- 5 Male
6 Female
7 Non-binary, genderqueer, agender or a similar identity
8 Two-spirit
9 Prefer to self-describe (specify) _____
10 Prefer not to answer
11
12

13 6. Are you an Indigenous person originating from North America?
14

15 [If NO or Prefer not to answer, please proceed to Q9](#)

- 16 No
17 Yes
18 Prefer not to answer
19
20

21 7. Which of the following groups do you belong to? Please select all that apply.
22

23 [Only answer if Q6 = YES](#)

- 24 First Nations
25 Inuit
26 Metis
27 Non-status First Nations
28 Other Indigenous (specify) _____
29 Prefer not to answer
30
31
32

33 8. Do you live on reserve?
34

35 [Only answer if Q7 = First Nations](#)

- 36 Yes
37 No
38 Prefer not to answer
39
40

41 9. How would you describe your ethnicity or race? Please select all that apply.
42

43 If you are an Indigenous person and answered YES to Q6, select any other that apply.
44

- | | |
|---|--|
| 45 <input type="checkbox"/> White | <input type="checkbox"/> West Asian |
| 46 <input type="checkbox"/> South Asian | <input type="checkbox"/> Korean |
| 47 <input type="checkbox"/> Chinese | <input type="checkbox"/> Japanese |
| 48 <input type="checkbox"/> Black | <input type="checkbox"/> Prefer to self-describe (specify) |
| 49 <input type="checkbox"/> Filipino | _____ |
| 50 <input type="checkbox"/> Latin American | <input type="checkbox"/> Prefer not to answer |
| 51 <input type="checkbox"/> Arab | |
| 52 <input type="checkbox"/> Southeast Asian | |
| 53 | |
| 54 | |
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| 58 | |

1
2
3 10. What are the first three digits of your postal code?
4

5 _____ OR Prefer not to answer
6
7

8
9 11. What is the highest level of education you have completed?
10

- 11 Less than high school graduation
12 High school graduation
13 Trade certificate, vocational school, or apprenticeship training
14 Non-university certificate or diploma from a community college, CEGEP
15 University Bachelor's degree
16 University graduate degree (Master's, Doctorate, etc.)
17 Prefer not to answer
18
19

20 12. How many people live in your household, including yourself?
21

22 _____ OR Prefer not to answer
23
24

25
26 13. How many bedrooms are in your household?
27

28 _____ OR Prefer not to answer
29
30

31
32 14. How many bathrooms are in your household?
33

34 _____ OR Prefer not to answer
35
36

37
38 **Section 2: COVID-19**

39 15. Do you think you have had COVID-19?
40

41 [If NO or Prefer not to answer, please proceed to Q18](#)
42

- 43 No
44 Yes
45 Prefer not to answer
46
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1
2
3 16. Why do you think you have had COVID-19? Please select all that apply.
4

5 [Only answer if Q15 = YES](#)

- 6
7 Symptom review online
8 Symptom profile
9 Nasal/throat test result
10 Health care provider
11 Contact with case
12 Other (specify) _____
13 Prefer not to answer
14
15

16 17. Were you hospitalized due to COVID-19?
17

18 [Only answer if Q15 = YES](#)

- 19
20 No
21 Yes
22 Prefer not to answer
23

24 18. Have you ever been tested for an active COVID-19 infection (using nasopharyngeal/throat swab, saliva, or
25 gargle test)?
26

27 [If NO or Prefer not to answer, please proceed to Q21](#)

- 28
29 No
30 Yes
31 Prefer not to answer
32

33 19. If yes, how many times have you been tested?
34

35 [Only answer if Q18 = YES](#)

36 _____ OR Prefer not to answer
37
38

39 20.1 Answer the following questions about the **first COVID-19 test**, if applicable.
40

41 20.1.a What was the date of the **first** test?
42

43 _____ DD / _____ MO / _____ YR
44

45 20.1.b What was the result of the **first** test?
46

- 47 Negative
48 Positive
49 Don't know
50
51
52
53
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1
2
3 20.1.c Did you have any symptoms of COVID when you had this test?
4

- 5 No
6 Yes
7 Don't know
8
9

10 20.1.d If yes, what symptoms did you have?
11

12 [Only answer if Q20.1.c = YES](#)
13

- 14 Cough
15 Fever
16 Shortness of breath
17 Sore muscles
18 Headache
19 Sore throat
20 Diarrhea
21 Decreased sense of smell or taste
22 Other (specify) _____
23
24
25

26 20.2 Answer the following questions about the **second COVID-19 test**, if applicable.
27

28 20.2.a What was the date of the **second** test?
29

30 _____ DD / _____ MO / _____ YR
31

32 20.2.b What was the result of the **second** test?
33

- 34 Negative
35 Positive
36 Don't know
37

38 20.2.c Did you have any symptoms of COVID when you had this test?
39

- 40 No
41 Yes
42 Don't know
43
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3 20.2.d If yes, what symptoms did you have?
4

5 [Only answer if Q20.2.c = YES](#)
6

- 7
8 Cough
9 Fever
10 Shortness of breath
11 Sore muscles
12 Headache
13 Sore throat
14 Diarrhea
15 Decreased sense of smell or taste
16 Other (specify) _____
17
18
19

20 20.3 Answer the following questions about the **third COVID-19 test**, if applicable.

21 20.3.a What was the date of the **third** test?
22

23 _____ DD / _____ MO / _____ YR
24

25 20.3.b What was the result of the **third** test?
26

- 27 Negative
28 Positive
29 Don't know
30

31 20.3.c Did you have any symptoms of COVID when you had this test?
32

- 33 No
34 Yes
35 Don't know
36
37

38 20.3.d If yes, what symptoms did you have?
39

40 [Only answer if Q20.3.c = YES](#)
41

- 42
43 Cough
44 Fever
45 Shortness of breath
46 Sore muscles
47 Headache
48 Sore throat
49 Diarrhea
50 Decreased sense of smell or taste
51 Other (specify) _____
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3 20.4.a Have you **tested positive** for COVID-19 (using nasopharyngeal, throat swab, saliva or gargle test) on a
4 test that wasn't included the questions above (that is, on the **4th or later test**)?
5

6 [If NO, please proceed to Q21](#)

- 7
8 No
9 Yes
10

11 20.4.b If yes, what was the date the first time you tested positive?

12
13 [Only answer if Q20.4.a = YES](#)

14
15 ____ DD / ____ MO ____ YR
16
17

18
19 **Section 3: Exposure**

20
21 21.a Have you traveled outside of your home province since **January 2020**?

22 [If NO, please proceed to Q23](#)

- 23
24 No
25 Yes
26 Prefer not to answer
27

28
29 21.b If you think you had COVID, did you travel in the 6 months before your symptoms began?

30 [Only answer if Q15 = YES](#)

- 31
32 No
33 Yes
34 Prefer not to answer
35
36
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45
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22. What province(s)/territory(ies) or country(ies) did you travel to? Select all that apply.

Only answer if Q21.a or Q21.b = YES

- Alberta
- British Columbia
- Manitoba
- New Brunswick
- Newfoundland and Labrador
- Northwest Territories
- Nova Scotia
- Nunavut
- Ontario
- Prince Edward Island
- Quebec
- Saskatchewan
- Yukon

OR Prefer not to answer

List countries you travelled to (separated by a comma):

23.a Do you do either paid or unpaid work in an environment where you work in close proximity to other people?

If NO or Prefer not to answer, please proceed to Q24

- No
- Yes
- Prefer not to answer

23.b If yes, have you been working in any of the following occupations or worksites in the past year? Please select all that apply.

Only answer if Q23.a = YES

- | | |
|---|--|
| <input type="checkbox"/> Hospital or health care facility | <input type="checkbox"/> Pharmacy |
| <input type="checkbox"/> First responder (paramedic/firefighter/police officer) | <input type="checkbox"/> Hairdresser or barber |
| <input type="checkbox"/> Childcare worker | <input type="checkbox"/> Aesthetician |
| <input type="checkbox"/> Correctional officer | <input type="checkbox"/> Flight attendant |
| <input type="checkbox"/> Teacher or other school staff | <input type="checkbox"/> Factor worker |
| <input type="checkbox"/> Transit driver | <input type="checkbox"/> Other (specify) _____ |
| <input type="checkbox"/> Food service industry | <input type="checkbox"/> Prefer not to answer |
| <input type="checkbox"/> Grocery store | |

1
2
3 24.a How many times have you been in a gathering of 10 or more since **March 2020**?

4 _____ OR Prefer not to answer

5
6
7 24.b If you think you have had COVID, how many times were you in gatherings of more than 10 people in the 6
8 months before your symptoms began?

9
10 [Only answer if Q15 = YES](#)

11 _____ OR Prefer not to answer

12
13
14
15
16 **Section 4: Health and Health Behaviours**

17 25. Do you currently smoke tobacco?

- 18
19 No
20 Yes
21 Prefer not to answer
22
23

24 26. If yes, how often do you smoke tobacco?

25
26 [Only answer if Q25 = YES](#)

- 27 Less than daily
28 Daily
29
30

31 27. Do you currently use e-cigarettes (vape)?

- 32 No
33 Yes
34 Prefer not to answer
35
36

37 28. If yes, how often do you use e-cigarettes (vape)?

38
39 [Only answer if Q27 = YES](#)

- 40 Less than daily
41 Daily
42
43
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29. Have you been diagnosed by a physician with any of the following chronic medical conditions? Please provide an answer for each condition.

		Yes	No	Don't Know	Prefer not to answer
a.	Hypertension				
b.	Diabetes				
c.	Asthma				
d.	Chronic Lung Disease				
e.	Chronic Heart Disease				
f.	Chronic Kidney Disease				
g.	Liver Disease				
h.	Cancer				
i.	Chronic Blood Disorder				
j.	Immune Suppressed				
k.	Chronic Neurological Disorder				

30. What is your current weight (circle units)?

_____ kg / lbs OR Prefer not to answer

31. What is your current height?

____ . ____ ____ m OR ____ ft ____ ____ in OR Prefer not to answer

32. Do you have a family physician/primary care provider?

- No
 Yes
 Don't know
 Prefer not to answer

33. Do you usually get a flu shot?

- No
 Yes
 Prefer not to answer

34. Indicate if, or how often you have done the following since **March 2020**?

		Never	Rarely	Occasionally	Often	Always	Prefer not to answer	
a.	Worn a mask in public places							
b.	Practiced physical distancing in public places							
c.	Avoided crowded places/gatherings							
d.	Avoided common greetings (such as a handshake or hug)							
		Never	Rarely	Occasionally	Often	Always	N/A	Prefer not to answer
e.	Limited contact with people at higher risk (e.g., an elderly relative)							
		No	Yes	N/A	Prefer not to answer			
f.	Self-isolated because you thought you were infected with COVID-19							
g.	Self-quarantined because you may have been exposed to COVID-19, but did not show symptoms							

35. **If you think you have had COVID**, have you done the following in the **6 months before your symptoms began?** (indicate how often).

Only answer if Q15 = YES

		Never	Rarely	Occasionally	Often	Always	N/A	Prefer not to answer
a.	Worn a mask in public places							
b.	Practiced physical distancing in public places							
c.	Avoided crowded places/gatherings							
d.	Avoided common greetings (such as handshake or hug)							
e.	Limited contact with people at higher risk (e.g., an elderly relative)							
		No	Yes	N/A		Prefer not to answer		
f.	Self-isolated because you thought you were infected with COVID-19							
g.	Self-quarantined because you may have been exposed to COVID-19, but did not show symptoms							

Section 5: Vaccine

36. Have you been vaccinated against COVID-19? Answer YES if you have received at least one dose of the COVID-19 vaccine.

[If NO or Prefer not to answer, proceed to Q43](#)

- No
 Yes
 Prefer not to answer

37. How many doses of the COVID-19 vaccine have you received so far?

[Only answer if Q36 = YES](#)

- One
 Two
 More than two

38. When did you receive the **first dose** of the COVID-19 vaccine?

[Only answer if Q36 = YES](#)

____ DD / ____ MM / _____ YR

39. When did you receive the **second dose** of the COVID-19 vaccine?

[Only answer if Q37 = TWO or MORE THAN TWO](#)

____ DD / ____ MM / _____ YR

40. Which vaccine did you receive?

[Only answer if Q36 = YES](#)

- Pfizer and BioNTech mRNA vaccine
 Moderna mRNA vaccine
 AstraZeneca Oxford vaccine
 Other (specify) _____
 Janssen (Johnson & Johnson) vaccine
 Don't know
 Prefer not to answer

41. Were you pregnant when you received the vaccine?

[If NO or N/A, proceed to Q43](#)

- No
 Yes
 N/A

42. If yes, what trimester were you in when you received the vaccine?

Only answer if Q41 = YES

- First
 Second
 Third

Section 6: Cannabis Use

43. Have you used cannabis (even once) in the past 12 months?

If NO, proceed to the end of this questionnaire

- No
 Yes

43.a If yes, how do you use cannabis? Please check all that apply.

Only answer if Q43 = YES

	Yes	No
Smoked dried plant		
Vaporized		
Oil		
Pills		
Added to baked good or other foods		
Other (specify)		

43.b If you smoke cannabis, please specify how you smoked/took cannabis:

- I do not smoke cannabis (proceed to Q44)

	Yes	No
Smoked as joint		
Smoked as joint mixed with tobacco		
Smoked as pipe		
Smoked as water pipe (bong)		
Inhaled using a vaporizer		
Eaten (e.g. as brownies, cake, cookies, etc.)		
Other (specify)		

1
2
3 44. Which response **best** describes how often you **currently** use cannabis?
4

5 [Only answer if Q43 = YES](#)

- 6
7 Rarely (2-3 times a year)
8 Monthly
9 Weekly
10 Daily
11 More than once a day
12

13
14 45. How many grams per week do you consume?

15 [Only answer if Q43 = YES](#)

- 16
17 Less than 1 gram
18 1-5 grams
19 6-9 grams
20 10 or more grams
21 Unknown
22
23

24 46. If you smoke cannabis, on average how many joints/cigarettes do you smoke per day?
25

26 [Only answer if Q43 = YES](#)

27 _____ OR I do not smoke cannabis
28
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33 **END OF QUESTIONNAIRE**
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the CTN
CIHR Canadian
HIV Trials Network

le Réseau
Réseau canadien
pour les essais VIH des IRSC

CTN 328: HIV-COV

CITF CDE FOLLOW-UP QUESTIONNAIRE

This version is administered at Visits 2, 3, 4, 5, and at unscheduled visits

Please answer all questions unless otherwise indicated

Participant ID: _____

1. Date (DD-MMM-YYYY):

____ / ____ / _____

Section 1: COVID-19

2. Do you think you have had COVID-19 since your last visit?

If NO or Prefer not to answer, please proceed to Q5

- No
 Yes
 Prefer not to answer

3. Why do you think you have had COVID-19 since your last visit? Please select all that apply.

Only answer if Q2 = YES

- Symptom review online
 Symptom profile
 Nasal/throat test result
 Health care provider
 Contact with case
 Other (specify) _____
 Prefer not to answer

1
2
3 4. Since your last visit, have you been hospitalized due to COVID-19?
4

5 [Only answer if Q2 = YES](#)

- 6
7 No
8 Yes
9 Prefer not to answer
10

11
12 5. Since your last visit, have you been tested for an active COVID-19 infection (using nasopharyngeal/throat
13 swab, saliva, or gargle test)?
14

15 [If NO or Prefer not to answer, please proceed to Q8](#)

- 16
17 No
18 Yes
19 Prefer not to answer
20

21
22 6. If yes, how many times have you been tested since your last visit?
23

24 [Only answer if Q5 = YES](#)

25 _____ OR Prefer not to answer
26
27
28
29

30 7.1 Answer the following questions about the **first COVID-19 test since your last visit**, if applicable.
31

32 7.1.a What was the date of the **first** test?
33

34 _____ DD / _____ MO / _____ YR
35

36 7.1.b What was the result of the **first** test?
37

- 38 Negative
39 Positive
40 Don't know
41

42 7.1.c Did you have any symptoms of COVID when you had this test?
43

- 44 No
45 Yes
46 Don't know
47
48
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2
3 7.1.d If yes, what symptoms did you have?
4

5 Only answer if Q7.1.c = YES
6

- 7
8 Cough
9 Fever
10 Shortness of breath
11 Sore muscles
12 Headache
13 Sore throat
14 Diarrhea
15 Decreased sense of smell or taste
16 Other (specify) _____
17
18
19
20

21
22 7.2 Answer the following questions about the **second COVID-19 test since your last visit**, if applicable.

23 7.2.a What was the date of the **second** test?
24

25 _____ DD / _____ MO / _____ YR
26

27 7.2.b What was the result of the **second** test?
28

- 29 Negative
30 Positive
31 Don't know
32

33 7.2.c Did you have any symptoms of COVID when you had this test?
34

- 35 No
36 Yes
37 Don't know
38
39

40 7.2.d If yes, what symptoms did you have?
41

42 Only answer if Q7.2.c = YES
43

- 44 Cough
45 Fever
46 Shortness of breath
47 Sore muscles
48 Headache
49 Sore throat
50 Diarrhea
51 Decreased sense of smell or taste
52 Other (specify) _____
53
54
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58

7.3 Answer the following questions about the **third COVID-19 test since your last visit**, if applicable.

7.3.a What was the date of the **third** test?

___ DD / ___ MO / ___ YR

7.3.b What was the result of the **third** test?

- Negative
 Positive
 Don't know

7.3.c Did you have any symptoms of COVID when you had this test?

- No
 Yes
 Don't know

7.3.d If yes, what symptoms did you have?

Only answer if Q7.3.c = YES

- Cough
 Fever
 Shortness of breath
 Sore muscles
 Headache
 Sore throat
 Diarrhea
 Decreased sense of smell or taste
 Other (specify) _____

7.4.a Have you **tested positive** for COVID-19 since your last visit on a test that wasn't included the questions above (that is, on the **4th or later test**)?

If NO, please proceed to Q8

- No
 Yes

7.4.b If yes, what was the date the first time you tested positive since your last visit?

Only answer if Q7.4.a = YES

___ DD / ___ MO ___ YR

Section 2: Exposure

8. Have you traveled outside of your home province since your last visit?

- No
 Yes
 Prefer not to answer

9.a Since your last visit, have you worked (either paid or unpaid) in an environment where you work in close proximity to other people?

[If NO or Prefer not to answer, please proceed to Q10](#)

- No
 Yes
 Prefer not to answer

9.b If yes, have you been working in any of the following occupations or worksites since your last visit? Please select all that apply.

[Only answer if Q9.a = YES](#)

- Hospital or health care facility
 First responder (paramedic/firefighter/police officer)
 Childcare worker
 Correctional officer
 Teacher or other school staff
 Transit driver
 Food service industry
 Grocery store
 Pharmacy
 Hairdresser or barber
 Aesthetician
 Flight attendant
 Factor worker
 Other (specify) _____
 Prefer not to answer

10. How many times have you been in a gathering of 10 or more since your last visit?

_____ OR Prefer not to answer

Section 3: Vaccine

11. Have you been vaccinated against COVID-19 since your last visit? Answer YES if you have **received at least one dose of the COVID-19 vaccine since your last visit.**

If NO or Prefer not to answer, proceed to the end of this questionnaire

- No
- Yes
- Prefer not to answer

12. How many doses of the COVID-19 vaccine have you received since your last visit?

Only answer if Q11 = YES

- One
- Two
- More than two

13. When did you receive the **first dose** of the COVID-19 vaccine since your last visit?

Only answer if Q11= YES

___ ___ DD / ___ ___ MM / ___ ___ ___ YR

14. Which vaccine did you receive for this **first dose** since your last visit?

Only answer if Q11= YES

- Pfizer and BioNTech mRNA vaccine
- Moderna mRNA vaccine
- AstraZeneca Oxford vaccine
- Other (specify) _____
- Janssen (Johnson & Johnson) vaccine
- Don't know
- Prefer not to answer

15. Were you pregnant when you received this **first dose** since your last visit?

If NO or N/A, proceed to Q17

- No
- Yes
- N/A

1
2
3 16. If yes, what trimester were you in when you received this **first dose** since your last visit?

4
5 [Only answer if Q15 =YES](#)

- 6
7 First
8 Second
9 Third
10

11
12
13 17. When did you receive the **second dose** of the COVID-19 vaccine since your last visit?

14
15 [Only answer if Q12 = TWO or MORE THAN TWO](#)

16
17 ____ DD / ____ MM / ____ YR
18

19
20 18. Which vaccine did you receive for this **second dose** since your last visit?

21
22 [Only answer if Q12 = TWO or MORE THAN TWO](#)

- 23
24 Pfizer and BioNTech mRNA vaccine
25 Moderna mRNA vaccine
26 AstraZeneca Oxford vaccine
27 Other (specify) _____
28 Janssen (Johnson & Johnson) vaccine
29 Don't know
30 Prefer not to answer
31
32

33
34 19. Were you pregnant when you received this **second dose** since your last visit?

35
36 [If NO or N/A, proceed to the end of this questionnaire](#)

- 37
38 No
39 Yes
40 N/A
41
42

43
44 20. If yes, what trimester were you in when you received this **second dose** since your last visit?

45
46 [Only answer if Q19 =YES](#)

- 47 First
48 Second
49 Third
50
51

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53 **END OF QUESTIONNAIRE**
54

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-9
Objectives	3	State specific objectives, including any prespecified hypotheses	9-10
Methods			
Study design	4	Present key elements of study design early in the paper	10-11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10-15, Table 1
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	11-12
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A (No matching)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	13 , 15-17
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11 (SSO cohort-same time points and methods). 12-13, 15-16,
Bias	9	Describe any efforts to address potential sources of bias	14-15, 22-26 (limitations discussed)
Study size	10	Explain how the study size was arrived at	14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	19
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	14 , 19
		(b) Describe any methods used to examine subgroups and interactions	19

		(c) Explain how missing data were addressed	19
		(d) If applicable, explain how loss to follow-up was addressed	19
		(e) Describe any sensitivity analyses	19
Results			Protocol paper thus results not yet available
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A protocol paper results not yet available
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	22-26
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on	32

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	which the present article is based	
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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

For peer review only

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		(c) Explain how missing data were addressed	19
		(d) If applicable, explain how loss to follow-up was addressed	19
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Results			Protocol paper thus results not yet available
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
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Outcome data	15*	Report numbers of outcome events or summary measures over time	
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Key results	18	Summarise key results with reference to study objectives	N/A protocol paper results not yet available
Limitations			
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