

Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
- A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- The statistical test(s) used AND whether they are one- or two-sided
 - Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
- A description of all covariates tested
- A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
 - Give P values as exact values whenever suitable.*
- For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection

ddPCR data was collected using QuantaSoft (BioRad Laboratories, Inc., version 1.7.4.0917), flow cytometry data was collected using Attune NxT software (thermofisher scientific)

Data analysis

ddPCR data was collected using QuantaSoft (BioRad Laboratories, Inc., version 1.7.4.0917), flow cytometry data was analyzed using FlowJo software (Treestar, version 10.7.1). Statistical analysis was performed in Prism 9 for mac OS

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The datasets generated during and/or analyzed during the current study will be made available from the corresponding author on reasonable request.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

Life sciences Behavioural & social sciences Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

| | |
|-----------------|---|
| Sample size | Our sample sizes of n=13 (New York) and n=16 (Vancouver) were determined by the participants who we were able to enroll in our study based on our inclusion and exclusion criteria. The suitability of the sample size to support our conclusions is demonstrated by the significant p values of the corresponding statistical tests. |
| Data exclusions | New York cohort: No data exclusions were performed. The V2 time point includes only 12 of 13 participants since one individual missed visit 2. Vancouver cohort: Results from one individual in an initial set of 16 participants were excluded on the basis of extremely poor viability and yield from the cryopreserved sample (9.9% viable, only 2,300 viable CD8+ events in flow cytometry file). |
| Replication | All ELISPOT, AIM+, and ddPCR assays were performed as technical replicates, and we observed good agreement between these - see ELISPOT examples in Figure 3. ELISAs were assessed with single wells for each dilution of plasma and each sample was run in a 7-point dilution series. |
| Randomization | A comparison between an HIV-negative and HIV-positive cohort is presented in the extended data as a non-conclusive observation. These were not randomized and this is stated as a caveat. |
| Blinding | Investigators were not formally blinded. |

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

| Materials & experimental systems | | Methods | |
|-------------------------------------|---|-------------------------------------|--|
| n/a | Involved in the study | n/a | Involved in the study |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> Antibodies | <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines | <input type="checkbox"/> | <input checked="" type="checkbox"/> Flow cytometry |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology | <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms | | |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> Human research participants | | |
| <input type="checkbox"/> | <input checked="" type="checkbox"/> Clinical data | | |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern | | |

Antibodies

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| Antibodies used | Flow antibodies: 1) anti-CD107a PE ((LAMP-1) Antibody Clone H4A3 Biolegend cat# 328608) 2)anti-CD3-Brilliant Violet 785 clone SK7 (cat# 344842), 3) anti-CD8-BV605 clone RPA-T8 (cat# 301040), 4) anti- CD137 (4-1BB) clone 4B4-1 (cat # 309810), 5) anti-OX40-Brilliant Violet 711 clone Ber-ACT35 (ACT35) (cat # 350030), 6) anti-CXCR5-AF488 clone J252D4 (cat # 356912), 7) anti-CD4-AF700 clone A161A1 (cat # 357418), 8) anti-CD69-APC-eFluor 780 clone FN50 (cat# 47-0699-42), ELISPOT antibodies: IFN-gamma and Granzyme B antibodies from Mabtech Interferon-gamma (cat # 3420-2A) and Granzyme B (cat # 3486-2A) enzyme-linked immune absorbent spot (ELISPOT) assays ELISA antibodies: peroxidase-conjugated goat anti-human IgG antibody (Jackson ImmunoResearch). Note that ELISAs also used the following recombinant protein (though not an antibody) recombinant YU-2 gp120 (provided by Dr. Mascola (VRC, NIH)) |
| Validation | Antibodies used for flow cytometry and ELISPOT were purchased from commercial suppliers and had been validated by suppliers and the authors in multiple experiments. Antibodies used for ELISA were obtained from the NIH or purchased from a commercial supplier and had been validated by suppliers and the authors in multiple experiments. |

Human research participants

Policy information about [studies involving human research participants](#)

| | |
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| Population characteristics | Relevant population characteristics including covariate summary statistics are provided in Table 1 and Extended Data Tables 1, 2, and 5. |
| Recruitment | <p>Study participants with HIV were recruited at Weill Cornell Medicine's Uptown or Chelsea Clinical Research Site. The Institutional Review Board at Weill Cornell Medicine approved this study (IRB# 21-02023358). Informed consent was obtained from all participants. Inclusion criteria were 18-89 years of age, people living with HIV with sustained HIV suppression for at least one year, HIV viral load <50 copies/mL within 12 months prior to baseline visit and planned receipt of vaccination with an mRNA-based SARS-CoV-2 vaccine. Exclusion criteria included contraindication to receipt of SARS-CoV-2 vaccination, plasma HIV RNA >200 copies/mL within one year prior to the baseline visit, known anemia with a hemoglobin < 10 gm/dL, prior receipt of SARS-CoV-2 vaccination, and discontinuation of ART for 7 or more consecutive days within the prior. Blood samples used in this study were collected at the baseline visit up to 6 weeks prior to planned vaccination, 2 weeks after the first vaccine dose, and 2 weeks after the second vaccine dose. Participants completed a post-vaccine side effects survey after receipt of each dose. Results were recorded and stored in REDCap. Blood was collected via phlebotomy in gold top serum separator tubes (SST) for anti-S SARS-CoV-2 serology, pearl top plasma preparation tubes (PPT) for HIV viral load, or ethylenediaminetetraacetic acid (EDTA) tubes for PBMC processing. HIV viral load and anti-S SARS-CoV-2 serology were performed by the New York-Presbyterian Hospital clinical laboratory.</p> <p>Deidentified samples from adults without HIV were obtained from the Rockefeller University (IRB protocol DRO-1006). Eligible participants were healthy adults with no history of infection with SARS-CoV-2, as determined by clinical history and confirmed through serology testing, receiving one of the two Moderna (mRNA-1273) or Pfizer-BioNTech (BNT162b2).</p> <p>Our independent validation cohort consisted of a subset (n=16) of study participants from a longitudinal study based in Vancouver, Canada 1. Of the 100 PLWH participants in the Vancouver cohort, 16 were selected based on sample availability and sufficient PBMC count at the time for validation purposes in this study. Ethical approval was granted through the University of British Columbia/ Providence Health Care and Simon Fraser University Research Ethics Boards. Informed consent was obtained from all participants. Vancouver participants had samples collected from baseline (pre-vaccine, V1), one month after SARS CoV-2 mRNA vaccine dose 1 (V2; median 31, range 28-37, Q1-Q3 30-32.5), and one month after vaccine dose 2 (V3; median 30, range 27-32, Q3-Q3 29-30) (Table 1). The time between doses 1 and 2 were median 54, range 49-61, Q1-Q3 51.5-57.5.</p> |
| Ethics oversight | Ethics approval to conduct this study was obtained from the Institutional Review Boards of Weill Cornell Medicine and the Rockefeller University, or the Research Ethics Board of the University of British Columbia/Providence Health Care and Simon Fraser University. All participants provided written informed consent. |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

| | |
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| Clinical trial registration | N/A - Not an interventional study |
| Study protocol | Sample collection protocols will be provided upon reasonable request. |
| Data collection | New York Cohorts: Clinical data were obtained from participants' medical records through EPIC, and compiled between June to August 2021. Clinical data for Vancouver cohort was obtained from the British Columbia (BC) Centre for Excellence in HIV/AIDS Drug Treatment Program Database, which houses clinical records for all PLWH receiving care in BC. |
| Outcomes | N/A - Not an interventional study |

Flow Cytometry

Plots

Confirm that:

- The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- All plots are contour plots with outliers or pseudocolor plots.
- A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

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| Sample preparation | Peripheral blood mononuclear cells were isolated from leukapheresis material by Ficoll gradient centrifugation. 10x10 ⁶ |
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| Sample preparation | PBMCs from each study participant collected at visits one, two, and three were thawed and rested for 3 hours at 37 °C 5% CO ₂ in R-10 medium (RPMI 1640 supplemented with 10% FBS, L-glutamine, and PenStrep). Additional experimental details are given in the AIM Assay section of "Methods." |
| Instrument | Attune NxT Flow Cytometer from ThermoFisher Scientific |
| Software | Data were collected with software Attune NxT Software version 3.1, and analyzed with software FlowJo version 10.4.2 |
| Cell population abundance | Shown in Figure 2. |
| Gating strategy | All samples were initially gated using forward scatter and side scatter to identify events corresponding to lymphocytes. Mononuclear cells were gated out of all events followed by gating live cells as Aqua Fluorescent Dye-, and then subsequent singlet gating. T-cells were gated as CD3+. The AIM+ (CD69+CD137+) CD4+ T-cells or CD8+ T-cells were gated from the CD3+ population, based on an unstimulated (DMSO) control. The entirety of the AIM+ gating for all of the samples studied is shown in Figure 2. The same gates were applied to all samples for any comparison. |

Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.