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Corresponding author(s): Ashish A. Sharma, Rafick-Pierre Sekaly

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

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	Sequencing data were acquired using Illumina HiSeq Control Software and BaseSpace Sequence Hub (Illumina) for whole-blood RNA-seq, and MGI DNBSEQ-T7 instrument software for single-cell RNA-seq data capture. Flow cytometry data were collected using FACSDiva (BD Biosciences) and stored as .fcs files. Plasma cytokine data were generated using the Methodological Mind acquisition software and quantified via Meso Scale Discovery (MSD) Workbench for standard curve fitting and concentration determination.
Data analysis	The following packages were used for downstream alignment and integration of omic data in R v4.4 (via RStudio v2024.04.1 Build 748). 1) For getting normalized transcript counts from sequencing FASTQ files: Trimmomatic (v0.39), STAR aligner(2.7.11b), HTSeq (v2.0.3) and 10x cloud CLI based Cell Ranger package (8.0.0). 2) Differential Gene Expression, cell deconvolution, Pathway Analyses and Enrichment Map: glmnet (v4.1), seurat (v5.0), fgsea (v3.19) and enrichmentmap (v3.4.0). 3) Data integration: mixOmics (v3.19). FlowJo (v 10.10.0) was used to analyze flow cytometry data and GraphPad Prism (v 10.2.3) was used for assessment of groups-wise comparisons and correlations for for smaller datasets (viral outcomes, module scores and cytokines). The figure panels were assembled using Adobe Illustrator 2024 (version 28.5). All code generated for the sequencing, omic (standalone and integration) analyses was generated using packages and pipelines cited above. The code will be published online as digital object on Zenodo (DOI: 10.5281/zenodo.11200738) upon finalization and before publication of the manuscript.

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 multiomic data collected in this manuscript include whole blood RNA-sequencing, single-cell RNA-sequencing, flow cytometry and plasma cytokines. As described in the methods, the sequencing data (FASTQs) from whole blood were generated on a Illumina HiSeq 2500 platform while the single-cell data were generated on the DNBseq-T7. Flow cytometry data was generated on a BD Symphony flow cytometer. Finally, the plasma cytokine data was generated on MesoScale Discovery platform. Expression set objects for all bulk RNA-sequencing data are accessible online as a digital object on Zenodo (DOI: 10.5281/zenodo.11200738). Cytokine, flow cytometry, transcriptome module scores, viral readouts, and clinical readouts are provided in Excel format in the supplementary material. All available bulk RNA-sequencing and single-cell RNA-sequencing FASTQ files are available on Gene Expression Omnibus under accession numbers GSE298837 and GSE298838, respectively.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex was reported for all participants enrolled in the CITN-12 trial (NCT02595866) based on self-reporting. Enrollment was symptom-based, with no exclusions based on sex and gender. ~90% of the participants were male. Informed consent was obtained from all participants for the publication of indirect identifiers, including exact sex. The demographics of the study population have been previously published (Uldrick et. al, Sci Trans Med 2022). The studies and procedures received approval from the Institutional Review Boards and each participating center.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were reported for all participants enrolled in the CITN-12 trial (NCT02595866). Enrollment was symptom-based, with no exclusions based on Race and ethnicity. ~25% of the participants were of the American American race, while 60% were of the White race; and 90% of the participants were not of the latino or hispanic ethnicity. Informed consent was obtained from all participants for the publication of indirect identifiers, including race and ethnicity. The demographics of the study population have been previously published (Uldrick et. al, Sci Trans Med 2022). The studies and procedures received approval from the Institutional Review Boards and each participating center.
Population characteristics	Age was reported for all participants enrolled in the CITN-12 trial (NCT02595866) and were identified as people with HIV and various cancers (both AIDS and non-AIDS associated cancers). The participants enrolled had a range of peripheral blood CD4 T cell counts and were sub-grouped into CD4 count based cohorts using the criteria shown in Figure 1 (also see Extended Figure 1 for full details of cancer type, CD4 counts and response to intervention). Enrollment was symptom-based, with no exclusions based on Age. The age of the participants ranged from 39 to 77 years (with a median of 55 years). Informed consent was obtained from all participants for the publication of indirect identifiers, including age. The demographics of the study population have been previously published (Uldrick et. al, Sci Trans Med 2022). The studies and procedures received approval from the Institutional Review Boards and each participating center.
Recruitment	All retrospective samples analyzed in this manuscript were collected from participants that were enrolled in and hence met the criteria for the the CITN-12 trial (NCT02595866).
Ethics oversight	The study protocol was approved by the Institutional Review Boards at Fred Hutch Cancer Center, the National Cancer Institute, New York University Langone Medical Center, Johns Hopkins University, Yale University, Mount Sinai School of Medicine, the University of California San Francisco (Zuckerberg and Parnassus campuses), Louisiana State University Health Sciences Center, the University of Alabama at Birmingham, Roswell Park Cancer Center, and the University of Maryland. All participants provided written informed consent.

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

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	The samples were collected as part of a Phase I clinical trial where safety of anti-PD1 in PWH and cancer was assessed. No sample size was defined for omic analyses apriori and all longitudinal samples collected during the first 1.5-2 years were selected for downstream multiomic analyses.

Data exclusions	Data was generated on all samples available. No data was excluded.
Replication	To ensure that mechanistic cascades were stringently defined, multiple orthogonal omic assays—including whole-blood RNA sequencing, plasma cytokine profiling, flow cytometry and single-cell RNA sequencing—were performed on the same set of samples at each time point and repeated longitudinally for each participant. Rigorous quality control criteria were applied across all platforms, including RNA integrity and library metrics for sequencing data, standard curve–based quantification and technical replicates for plasma cytokines, and comprehensive flow cytometry controls (unstimulated, stimulated, staining and compensation). The generalizability of transcriptomic signatures associated with responder status was assessed by examining the co-occurrence of responder-linked gene modules in publicly available single-cell RNA-sequencing databse. Finally, in vitro validation experiments were conducted to confirm these mechanisms at cellular and molecular levels.
Randomization	The samples were collected as part of the clinical protocol of the CITN-12 Phase I trial (NCT02595866) where all PWH and cancer were treated with anti-PD1. No randomization or further sample selection adjustments for co-variates was done for multiomic analyses of the samples from this study.
Blinding	The samples were collected as part of the clinical protocol of the CITN-12 Phase I trial (NCT02595866) where all PWH and cancer were treated with anti-PD1. No blinding was done for multiomic analyses of the samples from this study.

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

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

The details of all flow cytometry antibodies that were tested during the study are below. Note that the table is in comma-separated format.

Marker,Fluorophore,Staining Type,Volume (uL/50uL reaction),Clone,Catalog Number,Vendor

BCL2,BUV395,Intracellular,2.5,Bcl-2/100,563600 (Custom Conjugation),BD Bio
CD3,BUV496,Surface,0.5,UCHT1,612940,BD Bio
CD4,BUV563,Surface,0.25,L200,749214,BD Bio
CD45RA,BUV615,Surface,0.05,HI100,751555,BD Bio
CD27,BUV661,Surface,0.25,M-T271,741609,BD Bio
CD8,BUV737,Surface,0.125,SK1,612754,BD Bio
CD45RO,BUV805,Surface,1,UCHL1,748367,BD Bio
TCF7,BV421,Intracellular,0.5,C63D9,CS 9066S,CellSignaling
Live/Dead,BV480,Surface,0.125,-,TF L23105,ThermoFischer
CD14,BV480,Surface,0.5,MϕP9,566141,BD Bio
CD19,BV480,Surface,0.125,SJ25C1,566103,BD Bio
Ki67,BV570,Intracellular,0.25,Ki-67,570922 (Custom Conjugation),BD Bio
IRF4,BV605,Intracellular,0.5,Q9-343,566646 (Custom Conjugation),BD Bio
CD69,BV650,Surface,2.5,FN50,563835,BD Bio
EOMES,BV711,Intracellular,2.5,X4-83,567168 (Custom Conjugation),BD Bio
CCR7,BV750,Surface,0.25,3D12,746867,BD Bio
TBET,BV786,Surface,5,O4-46,564141,BD Bio
NR4A1,BB515,Intracellular,0.25,12.14,566735 (Custom Conjugation),BD Bio
SLAMF6,BB630,Surface,2.5,hSF6.4.20,566378 (Custom Conjugation),BD Bio
CD101,BB660,Surface,0.125,V7.1,566371 (Custom Conjugation),BD Bio
IFNg,BB700,Intracellular,0.25,B27,566394,BD Bio
TOX,PE,Intracellular,0.25,TXRX10,TF 12-6502-82,ThermoFischer
TNFa,PE-CF594,Intracellular,0.125,MAb11,562784,BD Bio
CD95,PE-Cy5,Surface,0.5,DX2,559773,BD Bio
PD1,PE-Cy7,Surface,0.125,MIH4,665124,ThermoFischer
ID2,APC,Intracellular,0.25,ILCID2,TF 17-9475-82,ThermoFischer
CD39,APC-Cy7,Surface,0.25,A1,328212,Biolegend
CD28,APC-R700,Surface,0.25,CD28.2,565181,BD Bio

Validation	Antibodies were commercially available and validated by the vendor prior to use.

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.

Clinical trial registration	Participants in this study were part of the Cancer Immunotherapy Trials Network-12 (CITN-12; NCT02595866), a multi-center, open-label, non-randomized, phase 1 study of participants (n=30) living with HIV and advanced cancer.
Study protocol	https://www.clinicaltrials.gov/study/NCT02595866
Data collection	Sample collection for the -omic work in this trial was initiated upon the start of the study (April 2016). Longitudinal biospecimens from 30 PWH were accrued and plasma + whole blood RNA-sequencing profiling experiments done in 2018-19. Single-cell experiments along with flow cytometry was done on available samples in 2021-22.
Outcomes	Unbiased integrated multiomic analyses was first done to define transcriptome and cytokine profiles altered 24 hours after anti-PD1 initiation. The treatment induced transcriptomic signatures were correlated with viral outcomes previously shown to be altered by treatment in the same trial (Uldrick et. al Sci Trans Med, 2022).

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A

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

Sample preparation	HIV-specific PBMC responses were assayed using flow cytometry. Following the thawing procedure, PBMCs were resuspended at 1.0 x 107 cells/ml and 100 µl, or 1.0 x 106 cells, were added per well of a 96-well U-bottom plate. Cells were either stimulated with media (unstimulated), 2 µg/ml of HIV-1 PTE GAG peptide, or 2 µg/ml of Staphylococcal enterotoxin B (SEB) in the presence of 10 µg/ml of brefeldin A (BFA). Following 6 hours of stimulation, cells were stained with live/dead stain to discriminate between live and dead cells. Following a wash with FACS buffer (PBS + 4% human serum), cells were incubated for 20 minutes at room temperature with a surface antibody staining cocktail mix that was diluted in Brilliant Stain Buffer (BD). For intracellular staining, cells were washed and incubated in fixation/permeabilization solution (FoxP3 Transcription Factor Kit, BD) for 30 minutes at 4ºC. Cells were then washed with fixation/permeabilization buffer and incubated with an intracellular antibody staining cocktail mix (prepared in fixation/permeabilization buffer) for 45 minutes at 4ºC. Following staining, cells were washed in FACS buffer, resuspended in 100 µl of PBS, and acquired on the BD FACS Symphony flow cytometer.
Instrument	BD FACSymphony A5
Software	BD FACSDiva was used to accrue data on the flow cytometer while FlowJo was used for downstream analyses
Cell population abundance	The analyses was performed on total peripheral blood mononuclear cells (PBMCs). No prior sorting was done.
Gating strategy	Gating was done in FlowJo. High quality events were first selected using the FlowAI plug-in. FSC/SSC gate was made on the lymphocyte population and singlets were selected based on FSC-H and FSC-A parameters. Live CD3+ cells were selected

followed by subgating for CD4+ and CD8+ T cells. The T cells were further divided into memory subsets based on the expression of CD45RA and CD27. Intracellular IFNg, TNFa and Ki67 positive cells were computed within each memory subset. A florescence minus one (FMO) control, an unstimulated (negative) and a SEB (positive) stimulation control was also included.

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