

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 Nikon Elements BR software (version 4.30.01), BD FACSDiva software (version 6.1.3), ChemiDoc MP Image Lab software (version 6.0.1, BioRad), QuantStudio3 Real-Time PCR System software (version 1.4.3, ThermoFisher)

Data analysis FlowJo software (version 10), ChemiDoc MP Image Lab software (version 6.0.1, BioRad), QuantStudio3 (ThermoFisher), FASTQC (version 0.11.1), STAR (version 2.5.2), Salmon (version 0.7.2), GSEA (version 2.2.3), Go Analysis (Go Panther 11.1), Sciex Analyst software (version 1.6.2), Geneious software (Biomatters), Discovery Workbench software (version 4.0, Meso Scale Delivery), R (version 3.5.0), GraphPad Prism (versions 6 and 8), Applied Biosystems 7500 Real-Time PCR software (version 2.0.6), Simplified Presentation of Incredibly Complex Evaluations (SPICE) software (version 6.0), Partek Genomics Suite software (version 6.6)

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research [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 list of figures that have associated raw data
- A description of any restrictions on data availability

Data availability

The data generated are available from corresponding authors 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](https://www.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	For BLT mouse studies, no statistical methods were used to predetermine sample size. At least 3 animals were used for each experimental group, the minimum to achieve statistical significance. Based on our previous data on SIV-infected ART-treated rhesus macaques, with a sample size of at least 7, we would be able to detect a significant difference between pre- and post- AZD5582 treatment samples in the levels of plasma RNA at the 0.05 significance level with a power of 0.90.
Data exclusions	Data exclusion was applied only to one RNAseq analysis represented on the heatmap of extended data Figure 7. One RM without on-ART viremia was excluded from this analysis for technical issues (higher than expected unmapped and multi-mapped reads, and lower than expected unique identified reads compared to the means).
Replication	In Figure 1b, symbols represent technical replicates of DMSO-normalized reporter signal induced by a dose titration of a panel of mono- and bivalent SMACm in a Jurkat luciferase reporter model of HIV-1 latency with 48 h exposure. In Extended Data Fig. 1f, fold induction of ncNF-kB target gene expression was measured by quantitative RT-PCR. Points represent two technical replicates. The data presented are representative of three independent experiments. In Extended Data Fig. 1g, for DMSO-normalized induction of luciferase activity from the Jurkat reporter model after exposure to AZD5582, points represent three replicates in one assay run, representative of several independent experiments. All attempts at replication were successful. In two independent experiments, plasma viremia was observed following AZD5582 administration to HIV-infected, ART-suppressed BLT mice. The use of non-human primates precludes our ability to replicate experiments. Sample sizes were chosen to maximize the likelihood of detecting statistical differences.
Randomization	For the study that examined the impact of AZD5582 administration on plasma and tissue viremia in BLT mice during ART suppression, mice were randomized for assignment to either experimental or control groups using randomization software available at random.org. For RM studies, peak plasma viral load (measured by standard assay) and plasma viral load before LRA intervention (as measured by ultrasensitive assay) were controlled for when allocated animals into experimental groups.
Blinding	Investigators were not blinded to group allocations or when assessing outcomes. In some instances, cells were pooled from individual humanized mice for each tissue and experimental group for the isolation of resting CD4+ T cells (Fig. 2).

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
<input type="checkbox"/>	<input checked="" type="checkbox"/> Antibodies
<input type="checkbox"/>	<input checked="" type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology
<input type="checkbox"/>	<input checked="" type="checkbox"/> Animals and other organisms
<input type="checkbox"/>	<input checked="" type="checkbox"/> Human research participants
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input type="checkbox"/>	<input checked="" type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Antibodies

Antibodies used

rat anti-mouse CD24-biotin (clone M1/69), BD Biosciences (Cat. # 557436), 10ug biotin-labeled rat anti-mouse CD24 antibody was adsorbed to 1mg streptavidin-labeled magnetic Dynabeads, <https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/mouse/purified-rat-anti-mouse-cd24-m169/p/557436>
anti-clAP1-unconjugated (clone EPR4673), Abcam (Cat. # 108361), 1:1,000 dilution, <https://www.abcam.com/ciap1-antibody-epr4673-ab108361.html>
anti-p100/p52-unconjugated (clone 18D10), Cell Signaling Technology (Cat. # 3017), 1:1,000 dilution, <https://www.cellsignal.com/products/primary-antibodies/nf-kb2-p100-p52-18d10-rabbit-mab/3017>
anti- $\text{I}\kappa\text{B}\alpha$ -unconjugated (clone 44D4), Cell Signaling Technology (Cat. # 4812), 1:1,000 dilution, <https://www.cellsignal.com/products/primary-antibodies/ikba-44d4-rabbit-mab/4812>

anti-clAP2-unconjugated (clone E40), Abcam (Cat. # ab32059), 1:1,000 dilution, <https://www.abcam.com/ciap2-antibody-e40-ab32059.html>

anti-beta-actin-HRP (clone AC-15), Abcam (Cat. # ab49900), 1:30,000 dilution, <https://www.abcam.com/beta-actin-antibody-ac-15-hrp-ab49900.html>

anti-clAP1-unconjugated (goat polyclonal IgG), R&D Systems (Cat. # AF8181, Lot # KH50516111), 10 ug/ml dilution, https://www.rndsystems.com/products/human-ciap-1-hiap-2-antibody_af8181

anti-CD3-BV421 (clone SP34-2), BD Biosciences (Cat. # 562877), 1:250 dilution, <https://www.bdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-human-antibodies/cell-surface-antigens/bv421-mouse-anti-human-cd3-sp34-2/p/562877>

anti-CD16-BV605 (clone 3G8), BD Biosciences (Cat. # 563172), 1:50 dilution, <https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/human/bv605-mouse-anti-human-cd16-3g8/p/563172>

anti-CD4-BV711 (clone L200), BD Biosciences (Cat. # 563913), 1:50 dilution, <https://www.bdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-non-human-primate-antibodies/cell-surface-antigens/bv711-mouse-anti-human-cd4-l200/p/563913>

anti-CD14-BV786 (clone M5E2), BD Biosciences (Cat. # 563698), 1:50 dilution, <https://www.bdbiosciences.com/us/applications/research/stem-cell-research/hematopoietic-stem-cell-markers/human/negative-markers/bv786-mouse-anti-human-cd14-m5e2/p/563698>

anti-CD123-PerCP-Cy5.5 (clone 7G3), BD Biosciences (Cat. #558714), 1:25 dilution, <https://www.bdbiosciences.com/us/applications/research/b-cell-research/surface-markers/human/percp-cy55-mouse-anti-human-cd123-7g3/p/558714>

anti-CD20-PE-CF594 (clone 2H7), BD Biosciences (Cat. # 562295), 1:500 dilution, <https://www.bdbiosciences.com/us/applications/research/stem-cell-research/hematopoietic-stem-cell-markers/human/negative-markers/pe-cf594-mouse-anti-human-cd20-2h7/p/562295>

anti-CD8-PE-Cy7 (clone SK1), BD Biosciences (Cat. # 335787), 1:500 dilution, <https://www.bdbiosciences.com/us/reagents/research/clinical-research--ruo-gmp/single-color-antibodies/pe-cytrade7-mouse-anti-human-cd8-sk1/p/335787>

anti-CD11c-Alexa700 (clone 3.9), Ebioscience (Cat. # 50-112-9413), 1:50 dilution, <https://www.thermofisher.com/antibody/product/CD11c-Antibody-clone-3-9-Monoclonal/56-0116-42>

anti-HLA-DR-APC-Cy7 (clone L243), BD Biosciences (Cat. # 335796), 1:50 dilution, <https://www.bdbiosciences.com/us/applications/research/stem-cell-research/mesenchymal-stem-cell-markers-bone-marrow/human/negative-markers/apc-cytrade7-mouse-anti-human-hla-dr-l243/p/335796>

anti-p100-unconjugated (clone EPR18756), Abcam (Cat. # ab191594), 1:25 dilution, <https://www.abcam.com/nfkb-p100nfkb2-antibody-epr18756-ab191594.html>

anti-CD45-APC (clone HI30), BD Biosciences (Cat. # 555485), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/human/apc-mouse-anti-human-cd45-hi30/p/555485>

anti-CD3-FITC (clone HIT3a), BD Biosciences (Cat. # 555339), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/t-cell-immunology/th-1-cells/surface-markers/human/fitc-mouse-anti-human-cd3-hit3a/p/555339>

anti-CD19-PE (clone HIB19), BD Biosciences (Cat. # 555413), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/clinical-research/oncology-research/blood-cell-disorders/surface-markers/human/pe-mouse-anti-human-cd19-hib19/p/555413>

anti-CD4-PerCP (clone SK3), BD Biosciences (Cat. # 347324), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/t-cell-immunology/th-1-cells/surface-markers/human/percp-mouse-anti-human-cd4-sk3-also-known-as-leu3a/p/347324>

anti-CD4-PE (clone RPA-T4), BD Biosciences (Cat. # 555347), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/t-cell-immunology/th-1-cells/surface-markers/human/pe-mouse-anti-human-cd4-rpa-t4/p/555347>

anti-CD8-PerCP (clone SK1), BD Biosciences (Cat. # 347314), 3 ul/test, <https://www.bdbiosciences.com/us/reagents/research/clinical-research--ruo-gmp/single-color-antibodies/percp-mouse-anti-human-cd8-sk1/p/347314>

anti-CD45-APC-Cy7 (clone 2D1), BD Biosciences (Cat. # 557833), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/human/apc-cy7-mouse-anti-human-cd45-2d1/p/557833>

anti-CD3-PE-Cy7 (clone SK7), BD Biosciences (Cat. # 557851), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/t-cell-immunology/th-1-cells/surface-markers/human/pe-cy7-mouse-anti-human-cd3-sk7-also-known-as-leu-4/p/557851>

anti-CD8-FITC (clone SK1), BD Biosciences (Cat. # 340692), 3 ul/test, <https://www.bdbiosciences.com/us/applications/clinical/blood-cell-disorders/asr-reagents/cd8-fitc-sk1/p/340692>

anti-CD38-APC (clone HB7), BD Biosciences (Cat. # 340439), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/t-cell-immunology/regulatory-t-cells/surface-markers/human/apc-mouse-anti-human-cd38-hb7/p/340439>

anti-HLA-DR-PE (clone TU36), BD Biosciences (Cat. # 555561), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/stem-cell-research/mesenchymal-stem-cell-markers-bone-marrow/human/negative-markers/pe-mouse-anti-human-hla-dr-tu36-also-known-as-t36-t36/p/555561>

anti-CD3-BV421 (clone UCHT1), BD Biosciences (Cat. # 562426), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/t-cell-immunology/th-1-cells/surface-markers/human/bv421-mouse-anti-human-cd3-ucht1-also-known-as-ucht-1-ucht-1/p/562426>

anti-HLA-DR-PerCP (clone L243), BD Biosciences (Cat. # 347364), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/stem-cell-research/mesenchymal-stem-cell-markers-bone-marrow/human/negative-markers/percp-mouse-anti-human-hla-dr-l243/p/347364>

anti-CD4-BV605 (clone RPA-T4), BD Biosciences (Cat. # 562658), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/t-cell-immunology/th-1-cells/surface-markers/human/bv605-mouse-anti-human-cd4-rpa-t4/p/562658>

anti-CD8-APC-Cy7 (clone SK1), BD Biosciences (Cat. # 557834), 3 ul/test, <https://www.bdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-human-antibodies/cell-surface-antigens/apc-cy7-mouse-anti-human-cd8-sk1/p/557834>

anti-CD25-APC (clone 2A3), BD Biosciences (Cat. # 340938), 3 ul/test, <https://www.bdbiosciences.com/us/applications/clinical/blood-cell-disorders/asr-reagents/cd25-apc-2a3/p/340938>

anti-CD45-V500 (clone H130), BD Biosciences (Cat. # 560777), 3 ul/test, <https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/human/v500-mouse-anti-human-cd45-hi30/p/560777>

anti-mouse IgG1k-APC (clone MOPC-21), BD Biosciences (Cat. # 555751), 3 ul/test, <https://www.bdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-human-antibodies/cell-surface-antigens/apc-mouse-igg1-isotype-control-mopc-21/p/555751>

anti-mouse IgG2ak-PerCP (clone X39), BD Biosciences (Cat. # 340765), 3 ul/test, <https://www.bdbiosciences.com/us/>

applications/clinical/blood-cell-disorders/asr-reagents/mouse-iggsub2asub-percp-x39/p/340765
 anti-mouse IgG1k-PE (clone MOPC-21), BD Biosciences (Cat. # 559320), 3 ul/test, <https://wwwbdbiosciences.com/us/applications/research/intracellular-flow/intracellular-antibodies-and-isotype-controls/anti-human-antibodies/pe-mouse-igg1-isotype-control-mopc-21/p/559320>
 anti-mouse IgG1k-PE-Cy7 (clone MOPC-21), BD Biosciences (Cat. # 557872), 3 ul/test, <https://wwwbdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-human-antibodies/cell-surface-antigens/pe-cy7-mouse-igg1-isotype-control-mopc-21/p/557872>
 anti-mouse IgG2ak-FITC (clone G155-178), BD Biosciences (Cat. # 553456), 3 ul/test, <https://wwwbdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-mouse-antibodies/cell-surface-antigens/fitc-mouse-igg2a-isotype-control-g155-178/p/553456>
 anti-CD3-APC-Cy7 (clone SP34-2), BD Biosciences (Cat. # 557757), <https://wwwbdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-non-human-primate-antibodies/cell-surface-antigens/apc-cy7-mouse-anti-human-cd3-sp34-2/p/557757>
 anti-Ki-67-AF700 (clone B56), BD Biosciences (Cat. # 561277), <https://wwwbdbiosciences.com/us/applications/research/intracellular-flow/intracellular-antibodies-and-isotype-controls/anti-human-antibodies/alexa-fluor-700-mouse-anti-ki-67-b56/p/561277>
 anti-HLA-DR-PerCP-Cy5.5 (clone G46-6), BD Biosciences (Cat. # 560652), <https://wwwbdbiosciences.com/us/applications/research/stem-cell-research/mesenchymal-stem-cell-markers-bone-marrow/human/negative-markers/percp-cy55-mouse-anti-human-hla-dr-g46-6/p/560652>
 anti-CCR5-APC (clone 3A9), BD Biosciences (Cat. # 550856), <https://wwwbdbiosciences.com/us/applications/research/t-cell-immunology/th-1-cells/surface-markers/human/apc-mouse-anti-human-cd195-3a9/p/550856>
 anti-CD8-BV711 (clone RPA-T8), BD Biosciences (Cat. # 563677), <https://wwwbdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-human-antibodies/cell-surface-antigens/bv711-mouse-anti-human-cd8-rpa-t8/p/563677>
 anti-CD4-BV650 (clone OKT4), Biolegend (Cat. # 317436), <https://www.biolegend.com/en-us/products/brilliant-violet-650-anti-human-cd4-antibody-7786>
 anti-PD-1-BV421 (clone EH12.2H7), Biolegend (Cat. # 329920), <https://www.biolegend.com/en-us/products/brilliant-violet-421-anti-human-cd279-pd-1-antibody-7191>
 anti-CD3-AF700 (clone SP34-2), BD Bioscience (Cat. # 557917), <https://wwwbdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-non-human-primate-antibodies/cell-surface-antigens/alexa-fluor-700-mouse-anti-human-cd3-sp34-2/p/557917>
 anti-CD69-PE-CF594 (clone FN50), BD Bioscience (Cat. # 562617), <https://wwwbdbiosciences.com/us/applications/research/t-cell-immunology/regulatory-t-cells/surface-markers/human/pe-cf594-mouse-anti-human-cd69-fn50-also-known-as-fn-50/p/562617>
 anti-CD25-PE-Cy7 (clone BC96), Biolegend (Cat. # 302612), <https://www.biolegend.com/en-us/products/pe-cy7-anti-human-cd25-antibody-1909>
 anti-CD45RA-PE-Cy7 (clone5H9), BD Biosciences (Cat. # 561216), <https://wwwbdbiosciences.com/us/applications/research/b-cell-research/surface-markers/non-human-primates/pe-cy7-mouse-anti-human-cd45ra-5h9/p/561216>
 anti-CD62L-PE (clone SKII), BD Biosciences (Cat. # 654666), <https://wwwbdbiosciences.com/us/applications/clinical/blood-cell-disorders/asr-reagents/cd62l-pe-sk11-also-known-as-anti-leu-8/p/654666>
 anti-CD95-BV605 (clone DX2), Biolegend (Cat. # 305627), <https://www.biolegend.com/en-us/products/brilliant-violet-605-anti-human-cd95-fas-antibody-8778>
 anti-CD28-PE-Cy5.5 (clone CD28.2), Beckman Coulter (Cat. # B24027), <https://www.beckman.com/reagents/coulter-flow-cytometry/antibodies-and-kits/single-color-antibodies/cd28/b24027>

Validation

The specificity of the antibodies purchased from commercial sources (BD Biosciences, Abcam, Cell Signaling Technology, R&D Systems, Ebioscience, Biolegend, and Beckman Coulter) were validated by the manufacturer as noted on their website (links provided above for each antibody).

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)	Jurkat Clone E6-1 cells (American Type Culture Collection TIB-152), TZM-bl cells (NIH AIDS Reagent Repository) and HEK 293T cells (European Collection of Authenticated Cell Cultures)
Authentication	Cell lines were authenticated by morphological identification and virus susceptibility profiles.
Mycoplasma contamination	Cell lines were tested negative for mycoplasma by the supplier
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used

Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals	BLT mice were constructed using 12-15 week old female NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ mice (NSG; The Jackson Laboratory, Bar Harbor, ME) mice. Female 20 week old BALB/cJ (The Jackson Laboratory, Bar Harbor, ME) were used for the serum chemistry analysis. Three healthy male rhesus macaques (<i>Macaca mulatta</i>) of Indian origin, age 6-7 years, were utilized for the AZD5582 pharmacokinetic study. Twenty-one male and female Mamu-B*08 and -B*17 negative rhesus macaques, age 3-6 years, were infected with SIVmac239 and treated with ART (Supplementary Table 7).
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Wild animals	The study did not involve wild animals.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	Mice were maintained under specific pathogen-free conditions by the Division of Comparative Medicine at the University of North Carolina, Chapel Hill. Mouse experiments were conducted in accordance with NIH guidelines for the housing and care of laboratory animals and in accordance with protocols reviewed and approved by the Institutional Animal Care and Use Committee at the University of North Carolina, Chapel Hill. Healthy Rhesus macaques for pharmacokinetic studies were housed at GlaxoSmithKline and all procedures were conducted in accordance with the GlaxoSmithKline Policy on the Care, Welfare, and Treatment of Laboratory Animals and were reviewed by the IACUC at GlaxoSmithKline. Rhesus macaques infected with SIV were housed at the Yerkes National Primate Research Center (Atlanta, GA) and treated in accordance with Emory University and Yerkes National Primate Research Center Institutional Animal Care and Use Committee regulations.

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

Human research participants

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

Population characteristics	Cells used in the QVOA and RNAseq experiments were obtained from participants stably suppressed on ART. At the time of sample donation, participants had a mean age of 43 years [range, 26-61 years], a mean duration on ART of 7 years [range, >6 months -22 years] and a mean CD4 count of 634 [range, 372-1364 cells/ μ l]. All participants were male, and 88% were Caucasians and 12% African American. Twenty-five percent of the participants were treated during acute infection and 75% during chronic infection.
Recruitment	Cells used in the QVOA assays were selected randomly across participants enrolled in a longitudinal reservoir measurement study and thus should not be subjected to self-selection bias. For the RNA seq experiments, cells from participants with a demonstrated increase in cell associated HIV RNA following ex-vivo exposure to AZD5582 were selected, potentially introducing a self-selection bias. However, given that these were global human gene expression measurements, we do not believe our results were impacted by this bias.
Ethics oversight	All human subjects samples were obtained under a specimen procurement protocol reviewed and approved by the University of North Carolina Biomedical Institutional Review Board and the McGill University Health Centre Ethical Review Board. Informed consent was obtained from all participants.

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

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	Sample preparation for the flow cytometric analysis of peripheral blood and tissues from humanized mice and rhesus macaques is detailed in the Methods section.
Instrument	Flow cytometry data was collected on BD LSRII, BD LSRFortessa, BD FACSAria LSR II, or BD FACSCanto instruments using BD FACSDiva software.
Software	Flow cytometry data was analyzed with FlowJo software.
Cell population abundance	Resting CD4+ T cells represented 0.12-9.48% (mean: 3.42%) of the total cell population. Prior to sorting of macaque resting CD4+ T cells by FACS, CD4+ T cells were enriched by magnetic bead selection. Post-sort purity was 97.8%.
Gating strategy	For the analysis of the frequency and phenotype of different human immune cell populations in the peripheral blood and tissues of BLT mice, an antibody specific for human CD45, a pan leukocyte marker, was used first to gate human leukocytes. Gates to define positive and negative populations were defined by isotype controls when appropriate.

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