Supplementary Table 1: Primers used in the SYBR green-based real-time PCR assay.

Marker	(5' → 3') Primer Sequence
ACTB (forward)	GAGAAAATCTGGCACCACACC
ACTB (reverse)	GGATAGCACAGCCTGGATAGCAA
NMNAT1 (forward)	CTGTGCCAAAGGTCAAGCTG
NMNAT1 (reverse)	GTGTTTCCACAGCACATCCG
NMNAT2 (forward)	CACGTTATCTTGCTCGCCTG
NMNAT2 (reverse)	AGGGTCCACCCTGATCCAAT
NMNAT3 (forward)	TAAGGGAGCGCAAGGTCAAG
NMNAT3 (reverse)	GCAGGATCTAGGCTGAAGCA
NAMPT (forward)	CCCAAGAGACTGCTGGCATA
NAMPT (reverse)	ATCGCTGACCACAGATACAGG
NAPRT (forward)	TGGACAGTGGTGACCTGCTA
NAPRT (reverse)	CCACCAGCTTATAGACGCCA
IL2RA (forward)	GGGACTGCTCACGTTCATCA
IL2RA (reverse)	TGCGGAAACCTCTCTTGCAT
HIV-1 (forward)	TACTGACGCTCTCGCACC
HIV-1 (reverse)	TCTCGACGCAGGACTCG
FOSL2 (forward)	GGCTCAGGCAGTGCATTCAT
FOSL2 (reverse)	CTCATCTCTCCTCCTGCGG
BTBD11 (forward)	CTCCAGCAAGCCGACAAATG
BTBD11 (reverse)	TCTCACAGTGTCGCTGCAAA
HCG27 (forward)	CCTCTGAGGGATGTCAAAGGC
HCG27 (reverse)	CAACACCTGCCTGAGCTTAC
IGSF9B (forward)	GAGATGTCAGAGATCACCCTGC
IGSF9B (reverse)	GCGTCTGTCCAAACACGTCC
NR4A2 (forward)	AGTCTGATCAGTGCCCTCGT
NR4A2 (reverse)	GATAGTCAGGGTTCGCCTGG
HMOX1 (forward)	ACTGCGTTCCTGCTCAACAT
HMOX1 (reverse)	TGGCATAAAGCCCTACAGCA

Supplementary Table 2: All reagents used in this study.

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
PE anti-human CCR5 (3A9), flow cytometry	BD Biosciences	Cat#556042; RRID: AB_396313
BV711 anti-human CCR5 (J418F1), flow cytometry	BioLegend	Cat#359130; RRID:AB_2734388
APC anti-human CD25 (M-A251), flow cytometry	BD Biosciences	Cat#555434; RRID:AB_398598
PE/Cy7 anti-human CD25 (BC96), flow cytometry	BioLegend	Cat#302612; RRID:AB_314282
PerCP/Cy5.5 anti-human CD25 (BC96), flow cytometry	BioLegend	Cat#302626; RRID:AB_2125478
BV605 anti-human CD25 (BC96), flow cytometry	BioLegend	Cat#302632; RRID:AB_11218989
PB anti-human CD3 (UCHT1), flow cytometry	BioLegend	Cat#300442; RRID:AB_2562048
FITC anti-human CD3 (UCHT1), flow cytometry	BioLegend	Cat#300405; RRID:AB_314059
BV785 anti-human CD3 (SK7), flow cytometry	BioLegend	Cat#344842; RRID: AB_2616891
PE anti-human CD38 (HB-7), flow cytometry	BioLegend	Cat#356604; RRID:AB_2561900
APC anti-human CD38 (HB-7), flow cytometry	BioLegend	Cat#356606; RRID:AB_2561902
APC/Cy7 anti-human CD4 (OKT4), flow cytometry	BioLegend	Cat#317418; RRID: AB_571947
PB anti-human CD4 (OKT4), flow cytometry	BioLegend	Cat#317429; RRID:AB_1595438
PerCP/Cy5.5 anti-human CD4 (OKT4), flow cytometry	BioLegend	Cat#317428; RRID:AB_1186122
FITC anti-human CD4 (OKT4), flow cytometry	BioLegend	Cat#317408; RRID:AB_571951
APC anti-human CD45 (HI30), flow cytometry	BioLegend	Cat#304037; RRID:AB_2562049
APC/Cy7 anti-human CD45 (2D1), flow cytometry	BioLegend	Cat#368516; RRID:AB_2566376
PE anti-human CD45 (2D1), flow cytometry	BioLegend	Cat#368510; RRID:AB_2566370
PE/Cy7 anti-human CD69 (FN50), flow cytometry	BioLegend	Cat#310912; RRID:AB_314847
APC anti-human CD69 (FN50), flow cytometry	BD Biosciences	Cat#560711; RRID:AB_1727507
PB anti-human CD69 (FN50), flow cytometry	BioLegend	Cat#310920; RRID:AB_493667
PE/Cy7 anti-human CD8 (SK1), flow cytometry	BioLegend	Cat#344712; RRID:AB_2044008
APC/Cy7 anti-human CXCR4 (12G5), flow cytometry	BioLegend	Cat#306527; RRID:AB_2565993
PE/Cy7 anti-human HLA-DR (LN3), flow cytometry	eBioscience™	Cat#25-9956-42; RRID:AB_1582284
BV785 anti-human HLA-DR (L243), flow cytometry	BioLegend	Cat#307642; RRID:AB_2563461
APC anti-human HLA-DR (L243), flow cytometry	BioLegend	Cat#307610; RRID:AB_314688

PE anti-human HLA-DR (L243), flow cytometry	BioLegend	Cat#307606; RRID:AB_314684
PerCP/Cy5.5 anti-human HLA-DR (L243), flow cytometry	BioLegend	Cat#307630; RRID:AB_893567
PE anti-human Ki-67 (20Raj1), flow cytometry	eBioscience™	Cat#12-5699-42; RRID:AB_10688373
FITC anti-HIV (KC57), flow cytometry	Beckman coulter	Cat#6604665; RRID:AB_1575987
PE anti-human Ki-67 (20Raj1), flow cytometry	eBioscience™	Cat#12-5699-42; RRID:AB_10688373
164Dy anti-Human CD161 (HP-3G10), mass cytometry	Fluidigm	Cat# 3164009B; RRID:AB_2687651
175Lu anti-Human CD279/PD-1 (EH12.2H7), mass cytometry	Fluidigm	Cat# 3175008B; RRID:AB_2687629
144Nd anti-Human CD195/CCR5 (NP-6G4), mass cytometry	Fluidigm	Cat# 3144007A; RRID:AB_2892770
153Eu anti-Human CD45RA (HI100), mass cytometry	Fluidigm	Cat# 3153001B; RRID:AB_2802108
165Ho anti-Human CD45RO (UCHL1), mass cytometry	Fluidigm	Cat#3165011B; RRID:AB_2756423
169Tm anti-Human CD25 (2A3), mass cytometry	Fluidigm	Cat# 3169003; RRID:AB_2661806
156Gd anti-Human CD183/CXCR3 (G025H7), mass cytometry	Fluidigm	Cat# 3156004B; RRID:AB_2687646
171Yb anti-Human CD185/CXCR5 (RF8B2), mass cytometry	Fluidigm	Cat# 3171014B; RRID:AB_2858239
158Gd anti-Human CD194/CCR4 (205410), mass cytometry	Fluidigm	Cat# 3158006A; RRID:AB_2687647
174Yb anti-Human CD4 (SK3), mass cytometry	Fluidigm	Cat# 3174004B; RRID:AB_2687862
176Yb anti-Human CD127/IL-7RA (A019D5), mass cytometry	Fluidigm	Cat# 3176004B; RRID:AB_2687863
141Pr anti-Human CD196/CCR6 (G034E3) , mass cytometry	Fluidigm	Cat# 3141003A; RRID:AB_2687639
154Sm anti-Human CD3 (UCHT1) , mass cytometry	Fluidigm	Cat# 3154003B; RRID:AB_2811086
159Tb anti-Human CD197/CCR7 (G043H7) , mass cytometry	Fluidigm	Cat# 3159003A; RRID:AB_2714155
173Yb anti-human CD184/CXCR4 (12G5), mass cytometry	Fluidigm	Cat# 3173001B; RRID:N/A
Y89 anti-human CD45 (HI30), mass cytometry	Fluidigm	Cat# 3089003B; RRID:AB_2661851
Bacterial and virus strains		
HIV-1_{JRFL} virus	NIH AIDS Reagent Program	Cat# ARP-395
Biological samples		
Blood samples from healthy donors	Hong Kong Red Cross	N/A
Blood samples from HIV-infected individuals	Shenzhen third People's Hospital or Prince of Wales Hospital	N/A
Chemicals, peptides, and recombinant proteins		
RPMI 1640 Medium, no glutamine	Gibco™	Cat# 21870092
Fetal Bovine Serum, qualified, Brazil	Gibco™	Cat# 10270106
GlutaMAX™ Supplement (L-glutamine)	Gibco™	Cat# 35050061

Penicillin-Streptomycin	Gibco™	Cat# 15140122
HEPES	Gibco™	Cat# 15630080
Recombinant Human IL-2 Protein	R&D Systems	Cat# 202-IL-050
Human IL-15	Miltenyi Biotech	Cat# 130-093-955
Efavirenz	Sigma-Aldrich	Cat# SML0536-10MG
Maraviroc	Sigma-Aldrich	Cat# PZ0002
RNAiso Plus	Takara	Cat# 9108
TaqMan™ Universal PCR Master Mix, no AmpErase™ UNG	Applied Biosystems™	Cat# 4364343
TB Green® Premix Ex Taq™ II (Tli RNase H Plus)	Takara	Cat# RR820A
Maxpar® Cell Staining Buffer	Fluidigm	Cat# 201068
Maxpar® Fix and Perm Buffer	Fluidigm	Cat# 201067
Maxpar® Cell Acquisition Solution	Fluidigm	Cat# 201240
Hoechst 33342 Solution	Thermo Scientific™	Cat# 62249
Opti-MEM	Thermo Scientific™	Cat# 31985070
Critical commercial assays		
RosetteSep™ Human CD4+ T Cell Enrichment Cocktail	Stemcell™ Technologies	Cat# 15062
Human CD4+ T cell Isolation kit	Miltenyi Biotec	Cat# 130-096-533
Human CD69 MicroBead Kit II	Miltenyi Biotec	Cat# 130-092-355
Human CD25 MicroBeads II	Miltenyi Biotec	Cat# 130-092-983
Human Anti-HLA-DR MicroBeads	Miltenyi Biotec	Cat# 130-046-101
Human Immunodeficiency Virus type 1 (HIV-1) p24 / Capsid Protein p24 ELISA Pair Set	Sino Biological	Cat# SEK11695-15
NAD/NADH-Glo™ Assay	Promega	Cat# G9071
CellTiter-Glo® Luminescent Cell Viability Assay	Promega	Cat# G7571
Nano-Glo® Luciferase Assay System	Promega	Cat# N1130
AllPrep DNA/RNA Mini Kit	Qiagen	Cat# 80204
QIAamp DNA Mini Kit	Qiagen	Cat# 51306
QIAamp Viral RNA Mini Kit	Qiagen	Cat# 52906
BD Cytofix/Cytoperm™ Fixation/Permeabilization Kit	BD Biosciences	Cat# 554714
PrimeScript™ II 1st Strand cDNA Synthesis Kit	Takara	Cat# 6210A
Lipofectamine™ RNAiMAX Transfection Reagent	Thermo Scientific™	Cat# 13778-030
Deposited data		
RNA-seq data	NCBI	GSE234308
Experimental models: Cell lines		
MOLT-4 $CCR5^+$ cell line	NIH AIDS Reagent Program	Cat# ARP-4984; RRID:N/A
ACH-2 cell line	Provided by Linqi Zhang (source from NIH AIDS Reagent Program)	Cat# ARP-349; RRID:N/A
HEK293T cell line	ATCC	Cat# CRL-3216; RRID:CVCL_0063
Experimental models: Organisms/strains		
NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ mouse	Laboratory Animal Unit of the University of Hong Kong	N/A
Oligonucleotides		
Lists of primers seen in Supplementary Table 1	BGI Genomics	N/A

HCG27 Silencer® Select pre-designed siRNA	Thermo Scientific™	Cat# S48397
Silencer® Select Negative Control #1 siRNA	Thermo Scientific™	Cat# 4404021
Recombinant DNA		
HIV-1 NL4-3 ΔEnv Vpr Luciferase Reporter Vector	NIH AIDS Reagent Program	Cat# ARP-3418

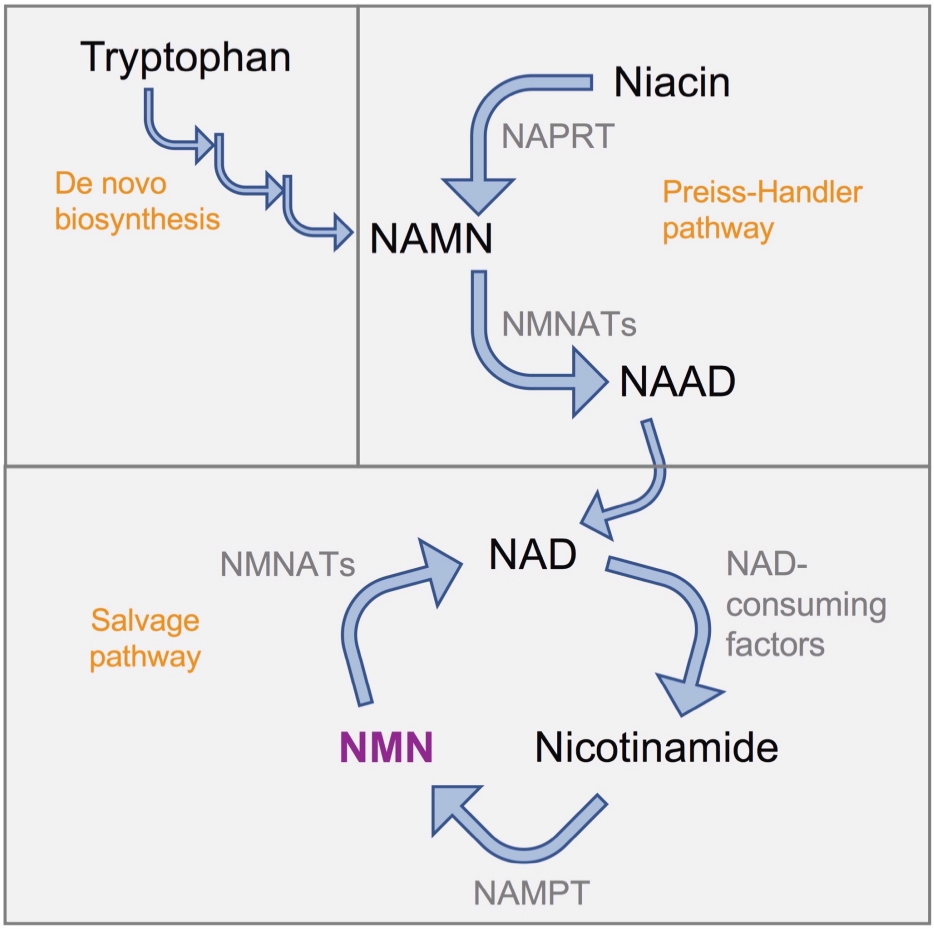
Supplementary Table 3: Author checklist based on ARRIVE guidelines.

Item		Recommendation	Section/line number, or reason for not reporting
Study design	**1**	For each experiment, provide brief details of study design including: a. The groups being compared, including control groups. If no control group has been used, the rationale should be stated. b. The experimental unit (e.g. a single animal, litter, or cage of animals).	**a. Line 259 & Fig. 6a** **b. Line 241**
Sample size	**2**	a. Specify the exact number of experimental units allocated to each group, and the total number in each experiment. Also indicate the total number of animals used. b. Explain how the sample size was decided. Provide details of any a priori sample size calculation, if done.	**a. Line 252-253, Fig. 6a** **b. Line 253-254**
Inclusion and exclusion criteria	**3**	a. Describe any criteria used for including and excluding animals (or experimental units) during the experiment, and data points during the analysis. Specify if these criteria were established a priori. If no criteria were set, state this explicitly. b. For each experimental group, report any animals, experimental units or data points not included in the analysis and explain why. If there were no exclusions, state so. c. For each analysis, report the exact value of n in each experimental group.	**a. No criteria were set** **b. No exclusions** **c. Each dot in Figure 6 represent each individual.**
Randomisation	**4**	a. State whether randomisation was used to allocate experimental units to control and treatment groups. If done, provide the method used to generate the randomisation sequence. b. Describe the strategy used to minimise potential confounders such as the order of treatments and measurements, or animal/cage location. If confounders were not controlled, state this explicitly.	**Randomisation and confounders were controlled by the single-blind design.**
Blinding	**5**	Describe who was aware of the group allocation at the different stages of the experiment (during the allocation, the conduct of the experiment, the outcome assessment, and the data analysis).	**Line 254; single-blind: the experimenter was aware of the group allocation.**
Outcome measures	**6**	a. Clearly define all outcome measures assessed (e.g. cell death, molecular markers, or behavioural changes). b. For hypothesis-testing studies, specify the primary outcome measure, i.e. the outcome measure that was used to determine the sample size.	**Line 493-535**
Statistical methods	**7**	a. Provide details of the statistical methods used for each analysis, including software used. b. Describe any methods used to assess whether the data met the assumptions of the statistical approach, and what was done if the assumptions were not met.	**Line 319-332**
Experimental animals	**8**	a. Provide species-appropriate details of the animals used, including species, strain and substrain, sex, age or developmental stage, and, if relevant, weight. b. Provide further relevant information on the provenance of animals, health/immune status, genetic modification status, genotype, and any previous procedures.	**Line 240-252**
Experimental procedures	**9**	For each experimental group, including controls, describe the procedures in enough detail to allow others to replicate them, including: a. What was done, how it was done and what was used. b. When and how often. c. Where (including detail of any acclimatisation periods). d. Why (provide rationale for procedures).	**Line 240-272 & Fig. 6a**
Results	**10**	For each experiment conducted, including independent replications, report: a. Summary/descriptive statistics for each experimental group, with a measure of variability where applicable (e.g. mean and SD, or median and range). b. If applicable, the effect size with a confidence interval.	**Line 493-535**

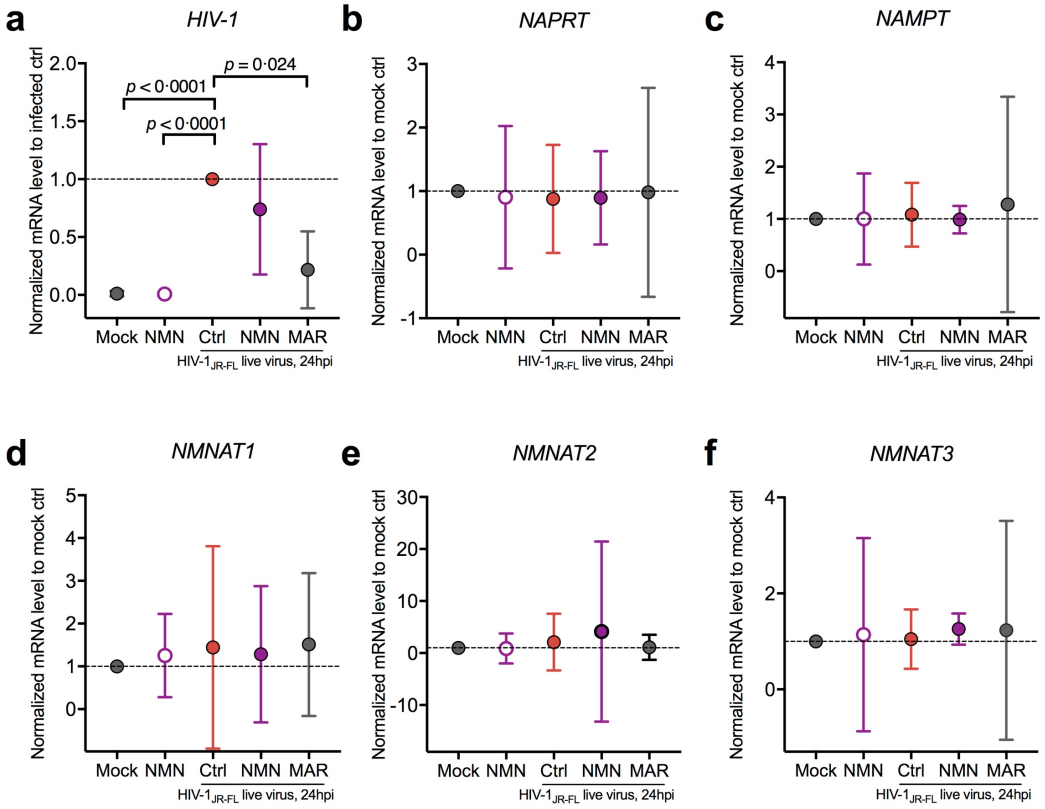
Abstract	**11**	Provide an accurate summary of the research objectives, animal species, strain and sex, key methods, principal findings, and study conclusions.	**Line 38-61**
Background	**12**	a. Include sufficient scientific background to understand the rationale and context for the study, and explain the experimental approach. b. Explain how the animal species and model used address the scientific objectives and, where appropriate, the relevance to human biology.	**a. Line 122-133** **b. Line 240-259 & Fig.6a**
Objectives	**13**	Clearly describe the research question, research objectives and, where appropriate, specific hypotheses being tested.	**Line 131-133** **Line 493-496**
Ethical statement	**14**	Provide the name of the ethical review committee or equivalent that has approved the use of animals in this study, and any relevant licence or protocol numbers (if applicable). If ethical approval was not sought or granted, provide a justification.	**Line 343-347**
Housing and husbandry	**15**	Provide details of housing and husbandry conditions, including any environmental enrichment.	**Line 240-243**
Animal care and monitoring	**16**	a. Describe any interventions or steps taken in the experimental protocols to reduce pain, suffering and distress. b. Report any expected or unexpected adverse events. c. Describe the humane endpoints established for the study, the signs that were monitored and the frequency of monitoring. If the study did not have humane endpoints, state this.	**a. Line 259-264** **b. N/A** **c. Line 259-262**
Interpretation/ scientific implications	**17**	a. Interpret the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature. b. Comment on the study limitations including potential sources of bias, limitations of the animal model, and imprecision associated with the results.	**a. Line 633-640 & Abstract** **b. Line 624-628 & 631-633**
Generalisability/ translation	**18**	Comment on whether, and how, the findings of this study are likely to generalise to other species or experimental conditions, including any relevance to human biology (where appropriate).	**Line 84-87**
Protocol registration	**19**	Provide a statement indicating whether a protocol (including the research question, key design features, and analysis plan) was prepared before the study, and if and where this protocol was registered.	**Protocols were reported in the cited paper.**
Data access	**20**	Provide a statement describing if and where study data are available.	**Line 662**
Declaration of interests	**21**	a. Declare any potential conflicts of interest, including financial and non-financial. If none exist, this should be stated. b. List all funding sources (including grant identifier) and the role of the funder(s) in the design, analysis and reporting of the study.	**a. Line 665** **b. Line 668-673**

Supplementary Table 4: The clinical information of ART-treated PLWH.

Patient ID	Gender	Age	CD4 count (cells/mm3)	Viral load (copies/mL)
1	F	32	761	<20
2	M	35	569	<20
3	M	65	375	<20
4	M	70	310	<20
5	M	52	760	<20
6	M	68	451	<20

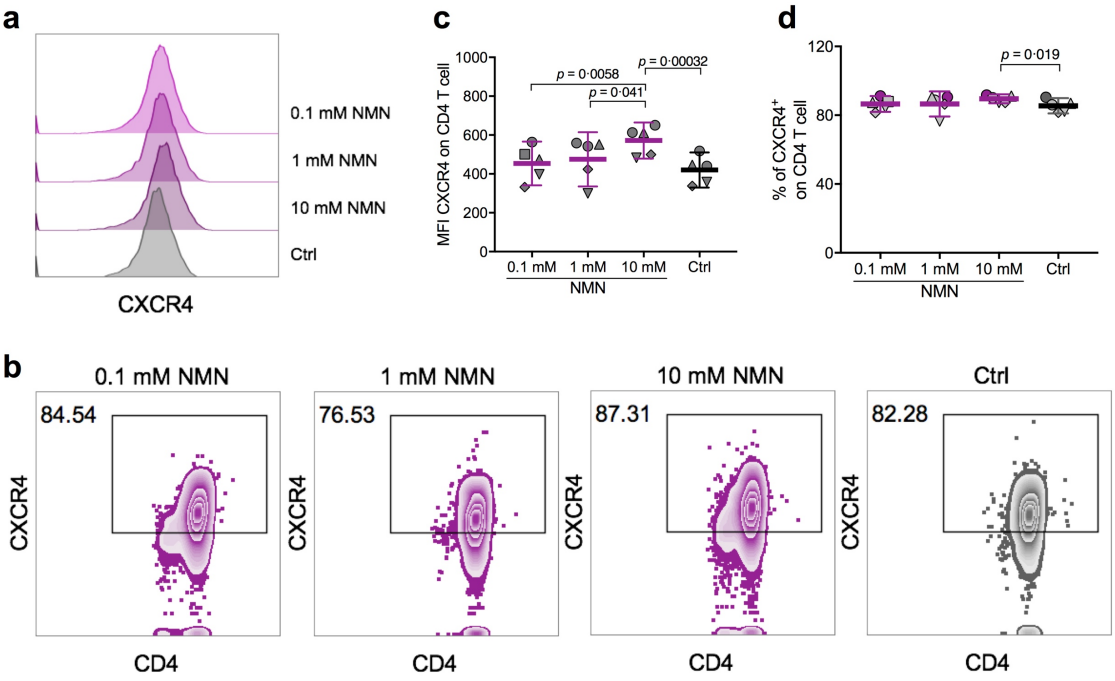


Supplementary Figure 1. The descriptive picture on three biosynthesis pathways of NAD.
NMN is the direct precursor of NAD in the salvage pathway. Nicotinamide is an indirect precursor and could be synthesized into NAD via enzymes including nicotinamide phosphoribosyltransferase (NAMPT) and nicotinamide mononucleotide adenylyltransferases (NMNATs) in the salvage pathway. Niacin can be catalysed into NAAD by nicotinate phosphoribosyltransferase (NAPRT) in the Preiss-Handler pathway before entering the salvage pathway. Tryptophan could be processed by de novo biosynthesis pathway before entering the Preiss-Handler pathway.

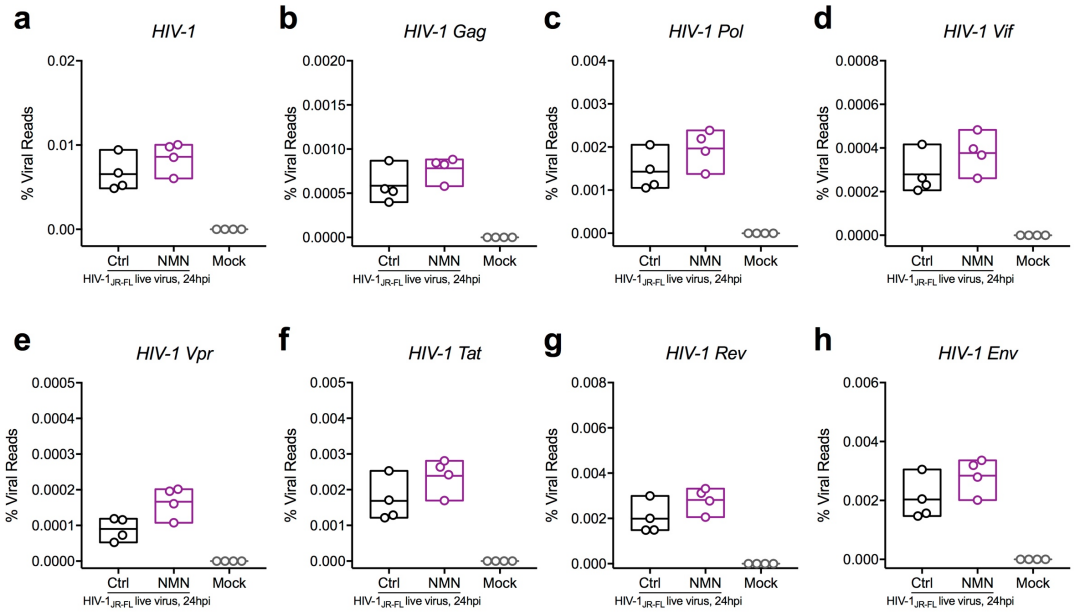


Supplementary Figure 2. NMN treatment or HIV infection does not alter the mRNA level of NMN-related metabolic enzymes. Related to Figure 1 and Figure 2.

MOLT-4 CCR5^{+} cells were infected with live HIV-1$_{JRFL}$ virus (2 ng p24 per 0·1 million cells). Maraviroc (MAR, 1 μM) pretreatment for 30 min before infection served as control. At 3 hours post-infection, cells were washed with PBS three times before adding fresh prepared RPMI media supplemented without or with 1 μM MAR or 10 mM NMN, in the presence of 10 U/mL IL-2. At 24 hours after treatment, cells were collected for real-time PCR assays on detecting mRNA level of HIV-1 **(a)** and NMN-related genes including *NAPRT* **(b)**, *NAMPT* **(c)**, *NMNAT1* **(d)**, *NMNAT2* **(e)**, *NMNAT3* **(f)**. Normalized NMN-related gene mRNA levels to mock control were calculated for genes except HIV-1, whereas normalized HIV-1 mRNA level to the infected control were calculated for HIV-1. Data represent Mean ± 95% CI; data passed normality test, and statistics were calculated based on a One-way ANOVA test with a post-hoc Turkey's test. Each dot represents one independent experiment.

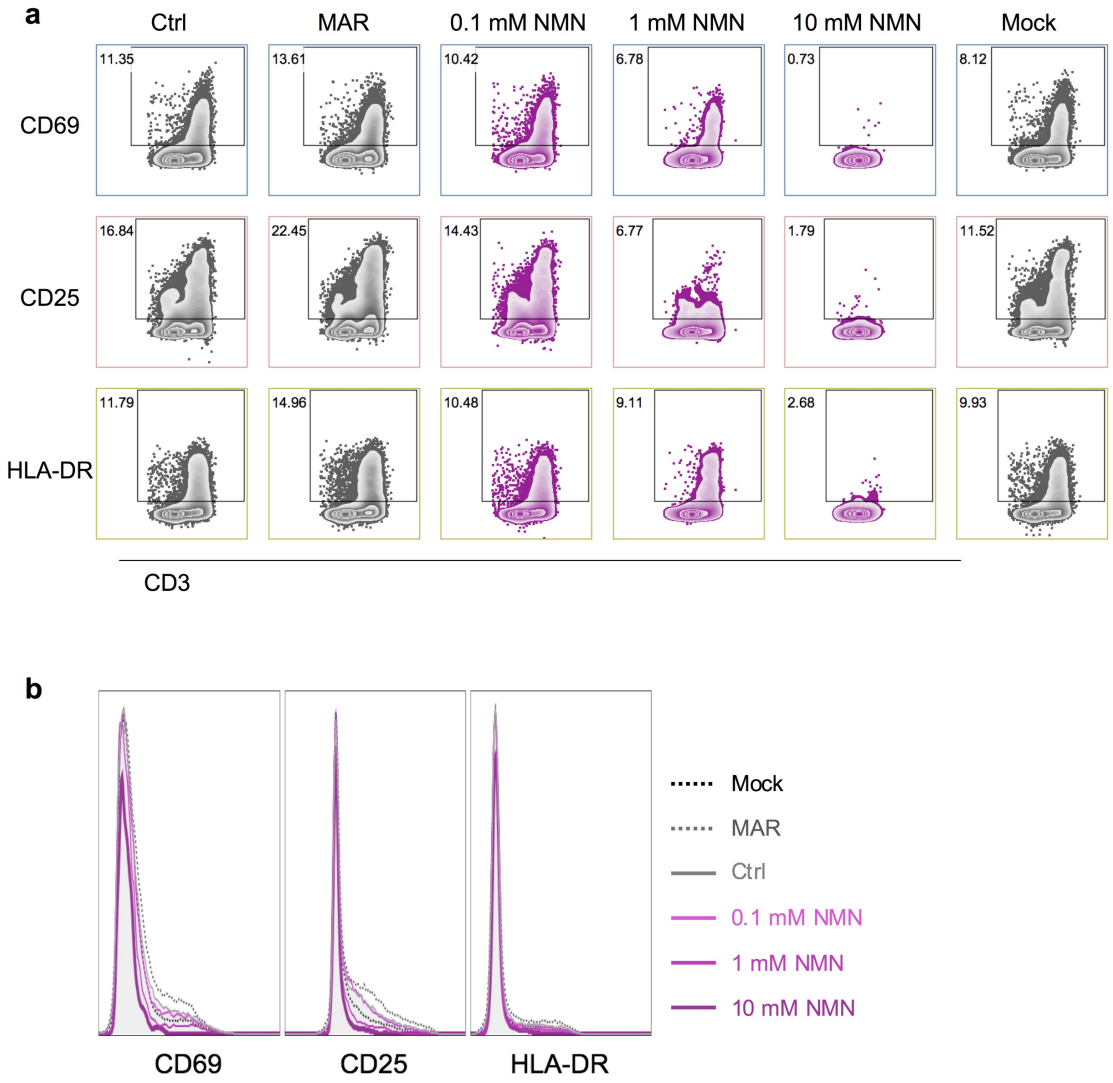


Supplementary Figure 3. Increase frequency and expression of CXCR4 on CD4$^+$ T cells under 10 mM NMN treatment. Related to Figure 2.
Purified human CD4$^+$ T Cells were treated with indicated compounds [NMN (0·1, 1, 10 mM) or PBS control] for five days and harvested for FACS analysis. **(a-b)** Representative histogram plots and FACS plots were displayed. The MFI **(c)** and frequency **(d)** of CXCR4 on CD4$^+$ T cells were compared among groups (n=5). Data represent Mean ± 95% CI; data passed normality test, and statistics were calculated based on a One-way ANOVA test with a post-hoc Turkey's test. Each dot represents one independent experiment.



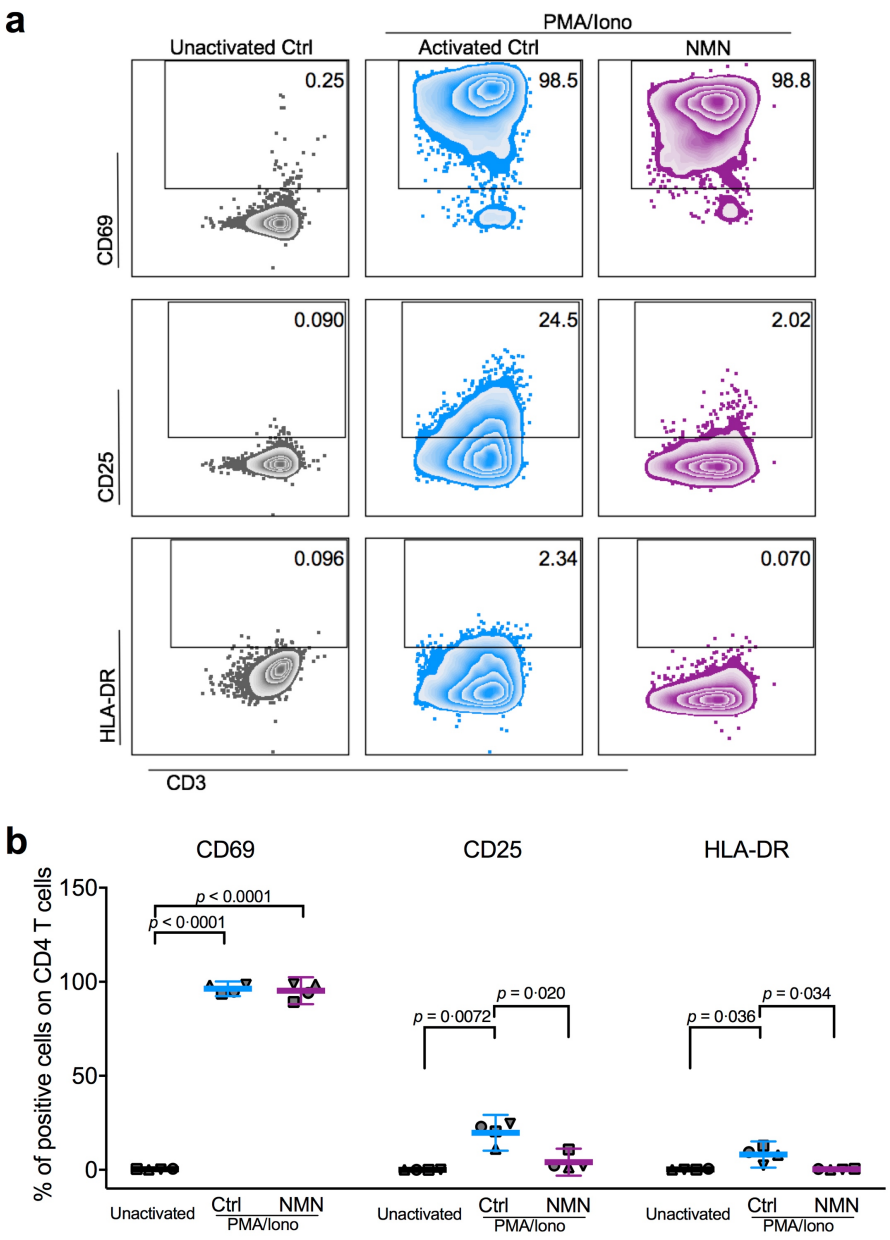
Supplementary Figure 4. NMN treatment did not change mRNA levels of HIV-1 full gene and its structural, regulatory and accessory genes. Related to Figure 2.

Purified primary $CD4^+$ T cells were treated with or without 10 mM of NMN for 24 hours before being infected with live $HIV\text{-}1_{JRFL}$ virus (2 ng p24 per 0·1 million cells) in the absence or presence of 10 mM of NMN for another 24 hours, followed by being harvested for bulk RNA-seq analysis. Clean reads were aligned to the HIV-1 genome (GenBank: U63632.1) using Hisat2 v2.2.1. The percentages of viral reads aligned to HIV-1 whole genome **(a)**, *HIV-1 Gag* **(b)**, *HIV-1 Pol* **(c)**, *HIV-1 Vif* **(d)**, *HIV-1 Vpr* **(e)**, *HIV-1 Tat* **(f)**, *HIV-1 Rev* **(g)** and *HIV-1 Env* **(h)** were calculated and compared. Data represent Mean with Min to Max in the floating bars.

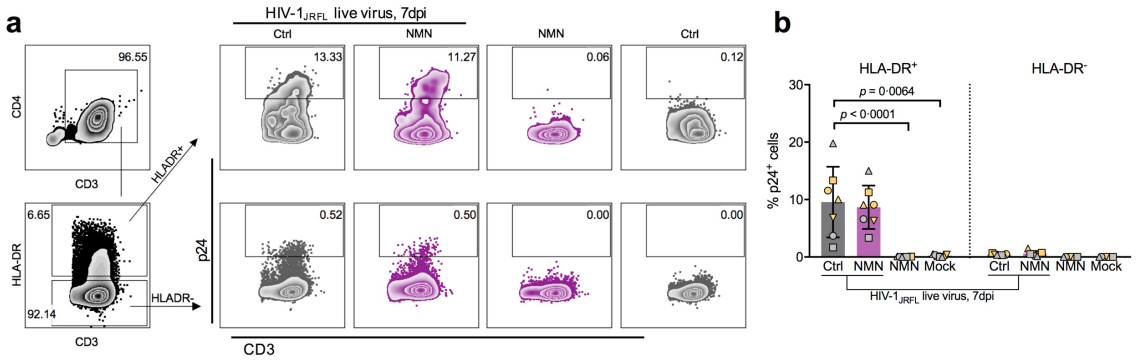


Supplementary Figure 5. Representative flow cytometry plots of JRFL-nLuc-infected NMN-treated CD4$^+$ T cells. Related to Figure 2.

Purified human CD4$^+$ T Cells were pre-treated without or with 1 μM Maraviroc (MAR) for 30 min. Cells were mocked infected or infected with HIV$_{JRFL}$-nLuc. At 24 hours post-infection, cells were washed and treated without or with 0·1, 1, 10 mM of NMN in the presence of IL-2 (10 ng/mL)/IL-15 (200 ng/mL) for 7 days. Vehicle-treated infected cells served as control (Ctrl), whereas mock cells serve as mock control. **(a)** Representative FACS plots on gating CD69$^+$, CD25$^+$, and HLA-DR$^+$ cells from CD4$^+$ T cells. **(b)** Representative histogram plots of CD69, CD25 and HLA-DR in flow cytometry analysis.

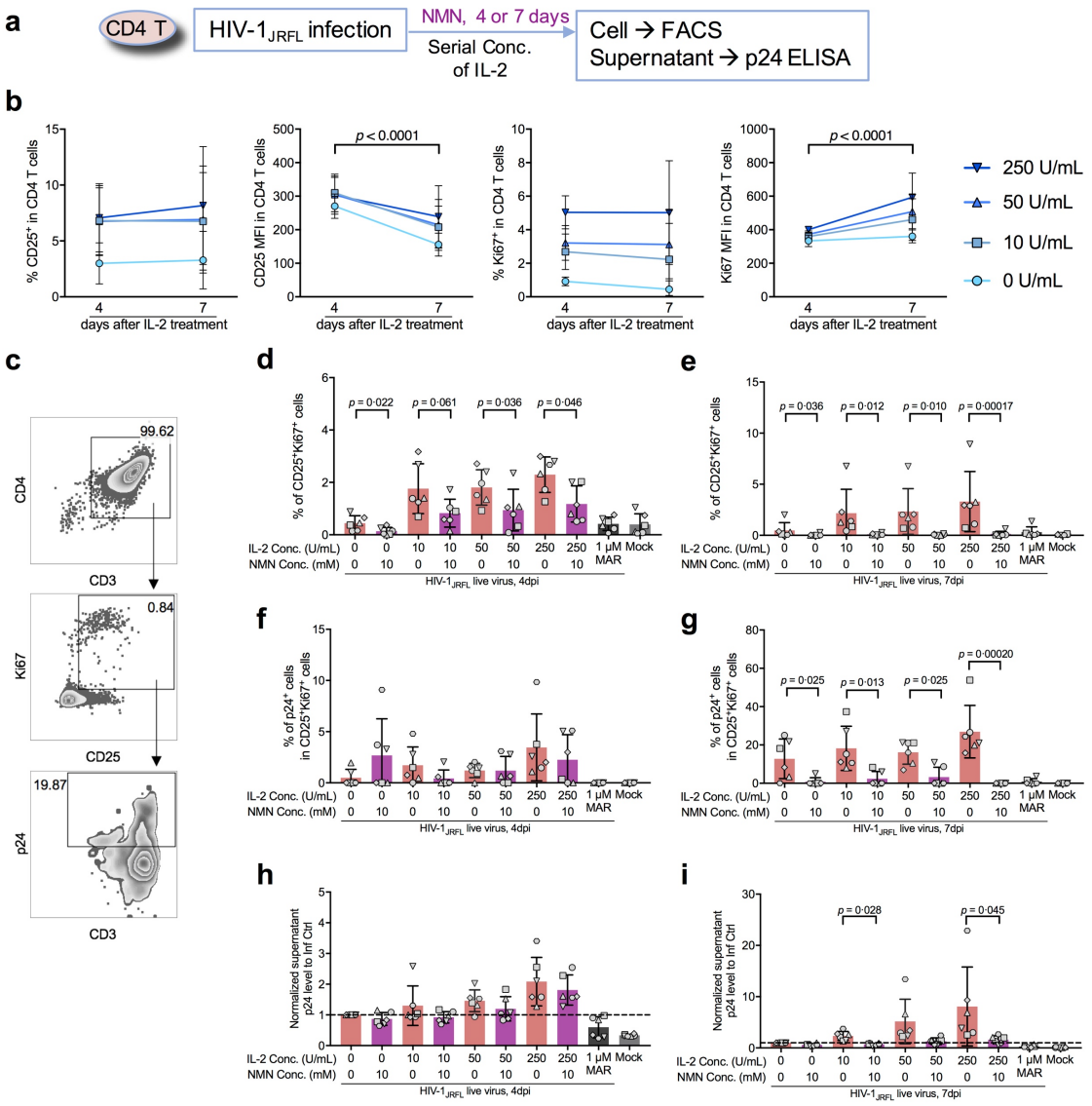


Supplementary Figure 6. Decreased percentage of CD25$^+$ and HLA-DR$^+$ CD4$^+$ T cells from HIV-uninfected donors under NMN treatment upon reactivation. Related to Figure 3.
Frozen PBMCs from 4 independent HIV-uninfected donors were used for resting CD4$^+$ T cell isolation. Purified resting CD4$^+$ T cells were treated with PMA (50 ng/mL) plus Ionomycin (1 µg/mL) (in short as PMA/Iono), PMA/Iono plus 10 mM NMN or mock, in the presence of 10 nM EFV and 10 U/ml IL-2 in one experiment. On day 4 after treatment, cells were collected for FACS analysis. **(a)** Representative FACS plots were displayed. **(b)** The percentage of CD69$^+$, CD25$^+$ and HLA-DR$^+$ cells on CD4$^+$ T cells was compared. Data represent Mean ± 95% CI; data passed normality test, and statistics were calculated based on paired Student's t-test. Each dot represents one independent individual.



Supplementary Figure 7. NMN did not alter the percentage of p24$^+$ cells in HLA-DR$^+$ or HLA-DR$^-$ CD4$^+$ T cells. Related to Figure 4.

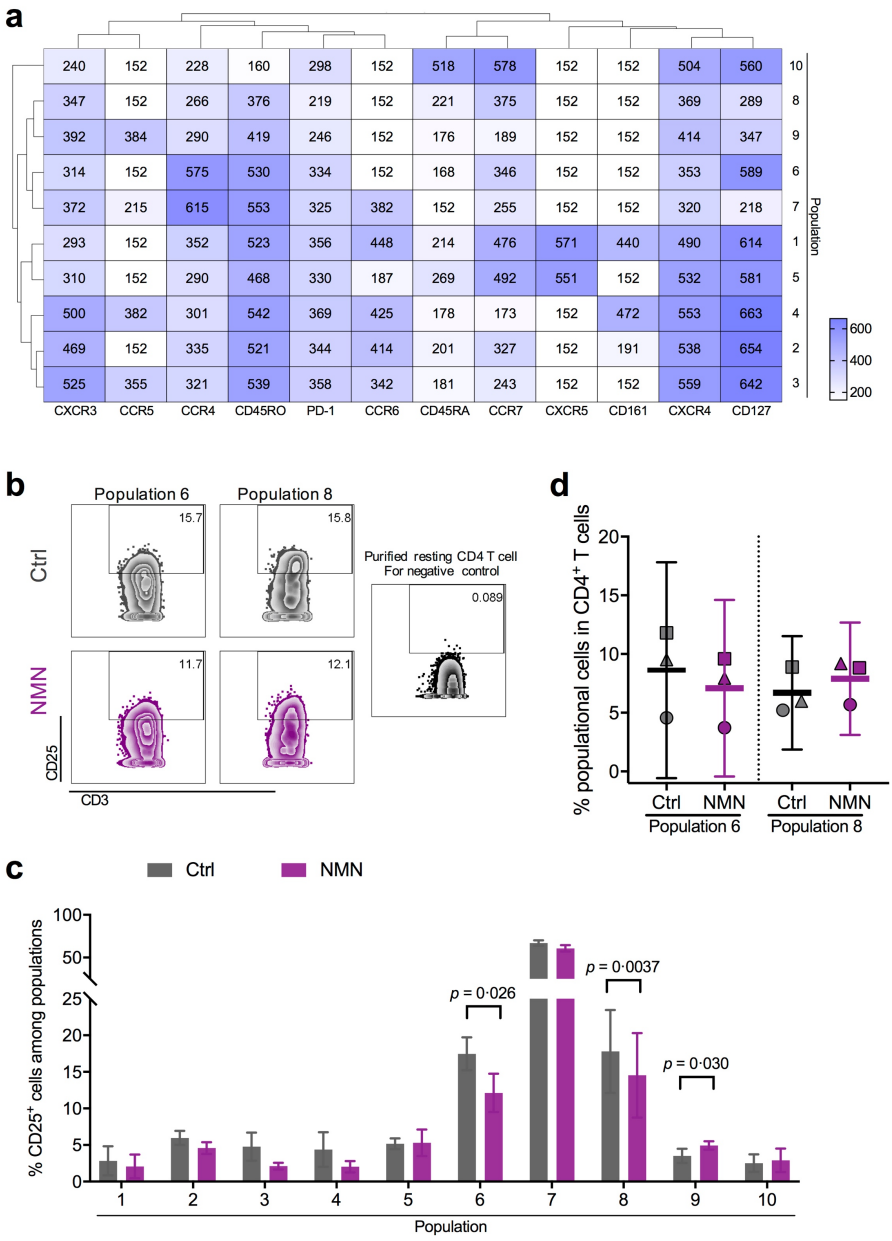
Primary CD4$^+$ T cells were isolated from PBMCs (n=7) and pre-treated with 10 mM of NMN for 24 hours before infection with live HIV-1$_{JRFL}$ virus (2 ng p24 per 0·1 million cells) or mock. After infection, cells were treated with 10 mM NMN for seven days. On Day 7 post-infection, cells were harvested for intracellular p24 staining and FACS analysis on CD25, HLA-DR, and ki67 expression. **(a)** The gating strategy on p24$^+$ cells in HLA-DR$^{+/-}$ CD4$^+$ T cells among groups was displayed with representative plots. **(b)** The percentage of p24$^+$ cells in HLA-DR$^{+/-}$CD4$^+$ T cells was compared. Data represent Mean ± SD; data did not pass normality test, and statistics were calculated using a Friedman test with an appropriate posthoc test. Each dot represents one independent individual.



Supplementary Figure 8. NMN significantly reduced p24$^+$ cells in CD25$^+$ki67$^+$ CD4$^+$ T cells on day 7 after the infection. Related to Figure 4.

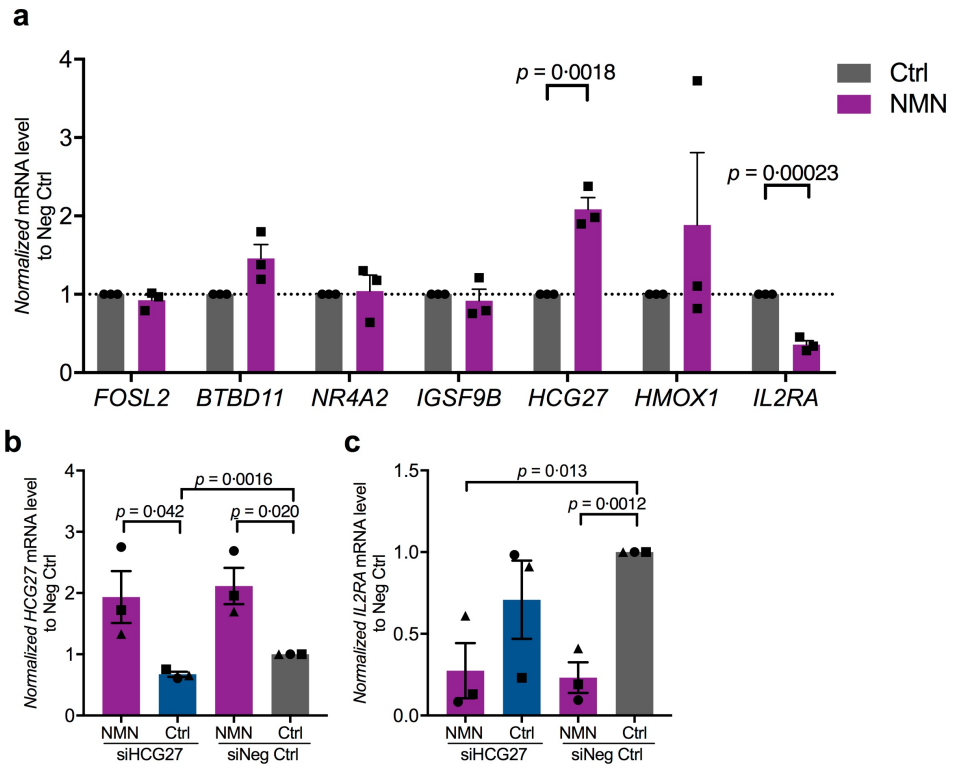
Primary CD4$^+$ T cells were isolated from PBMCs (n=6) and pre-treated without or with 1 μM Maraviroc (MAR) for 30 min before being infected with live HIV-1$_{JRFL}$ virus (2 ng p24 per 0·1 million cells) or mock. After infection, cells were treated with 10 mM NMN for seven days. On Day 7 post-infection, cells were harvested for intracellular p24 staining. **(a)** The experimental flowchart was displayed. **(b)** The frequencies and expression levels of CD25 and ki67 in CD4$^+$ T cells were assessed by flow cytometry. **(c)** The gating strategies on CD25$^+$ki67$^+$CD4$^+$ T cells and p24$^+$ cells in CD25$^+$ki67$^+$CD4$^+$ T cells. The percentage of CD25$^+$ki67$^+$ cells in CD4$^+$ T cells on day 4 **(d)** and day 7 **(e)** was compared among groups. The percentage of p24$^+$ cells in CD25$^+$ki67$^+$CD4$^+$ T cells on day 4 **(f)** and day 7 **(g)** was compared among groups. The normalized supernatant p24 levels to infection control on day 4 **(h)** and day 7 **(i)** was compared among groups.

Data represent Mean ± SD. For **(b)**, data passed normality test, and statistics were calculated using a Two-way ANOVA test followed by a Bonferroni's multiple comparisons test. For **(d),** data passed normality test, and statistics were calculated using a paired Student's t-test. For (**e-i**), data did not pass normality test, and statistics were calculated using a Friedman test without correction. Each dot represents one independent individual.

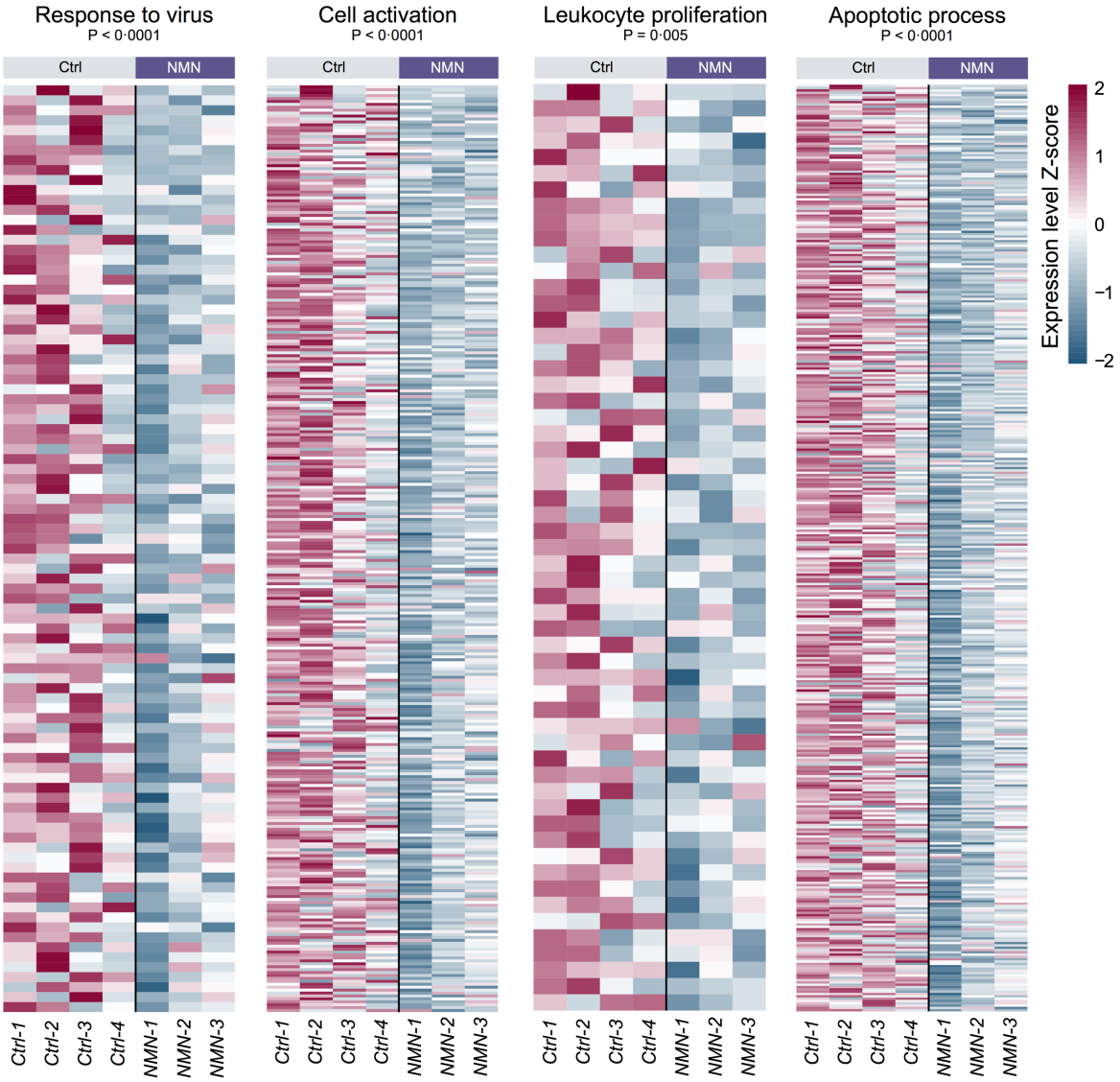


Supplementary Figure 9. Effect of NMN treatment on CD4$^+$ T cell subpopulations by CyTOF analysis. Related to Figure 4.

Purified CD4$^+$ T cells were isolated from fresh PBMCs of 3 independent healthy donors. Cells were treated with 10 mM NMN or vehicle for 4 days before being collected for CyTOF analysis on CD25$^+$ cells among various CD4$^+$ T cell subsets in one experiment. The t-SNE plot of CyTOF data was generated by opt-SNE using the KNN algorithm and the Fit-SNE gradient algorithm. Clustering was processed using the FlowSOM algorithm in order to obtain 10 populations (meta clusters). **(a)** The FlowSOM-generated heatmap displays the MFI of multiple markers per population. **(b)** Representative plots show the gating strategy on CD25$^+$ cells among populations. **(c)** The percentage of CD25$^+$ cells in all populations was compared between groups. **(d)** The percentage of these two populations in CD4$^+$ T cells was compared between the NMN group and the control group. Data represent Mean ± SD; data passed normality test, and statistics were calculated using a paired Student's t-test. Each dot represents one independent individual.

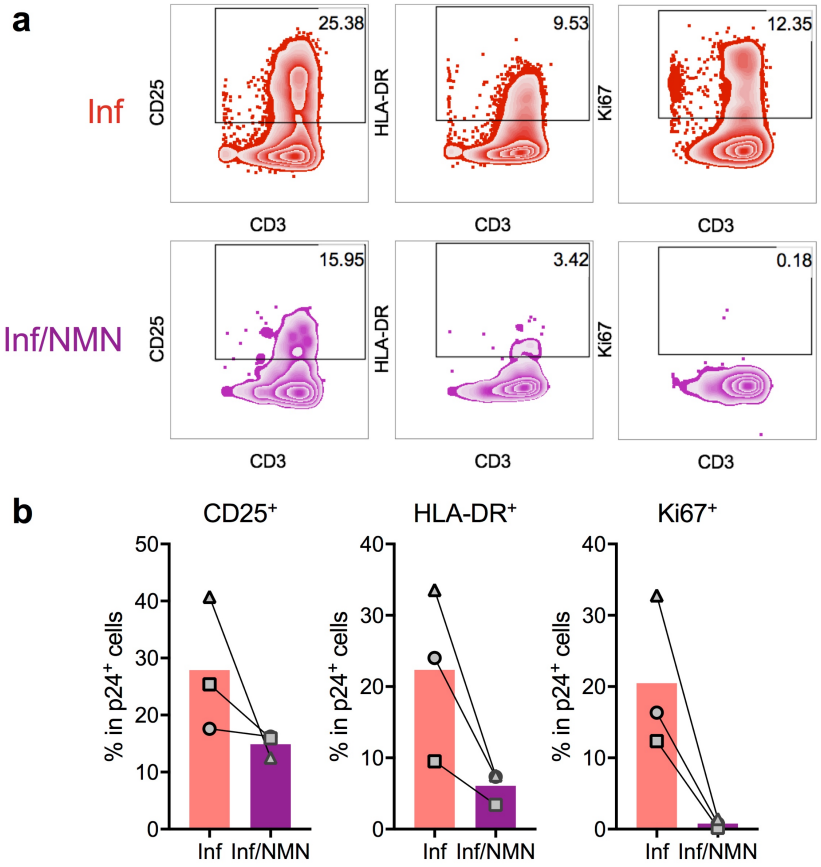


Supplementary Figure 10. The *in vitro* validation results on top modulated genes found by RNA-seq analysis. Related to Figure 5.
MOLT-4 CCR5^{+} cells were treated without or with 10 mM NMN for 24 hours before RNA extraction for qPCR assays on **(a)** the mRNA expression level of *FOSL2, BTBD11, NR4A2, IGSF9B, HCG27, HMOX1 and IL2RA.* MOLT-4 CCR5^{+} cells were transiently transfected with 10 nM of siHCG27 or control siRNA. At 48 hours after transfection, cells were treated without or with 10 mM NMN for additional 24 hours before RNA extraction for qPCR assay on the mRNA expression level of *HCG27* **(b)** and *IL2RA* (**c**, CD25). Data represent Mean ± SD; data passed normality test, and statistics were calculated using an unpaired Student's t-test. Each dot represents one replicated experiment.



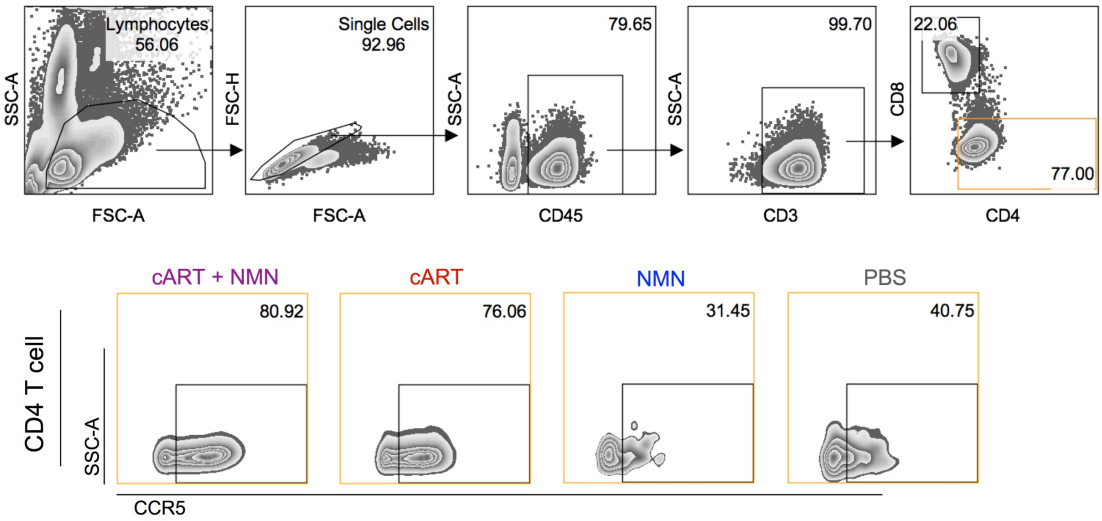
Supplementary Figure 11. The heatmap of some specific pathways affected by NMN treatment. Related to Figure 5.

Purified primary $CD4^+$ T cells were treated with (n=3) or without (n=4) 10 mM of NMN for 48 hours before harvesting for bulk RNA-seq analysis. CD25-related Gene Ontology (GO) of Gene Set Enrichment Analysis (GSEA) was performed. The heatmap of the specific pathways including responses to virus, cell activation, leukocyte proliferation and apoptotic process was displayed.

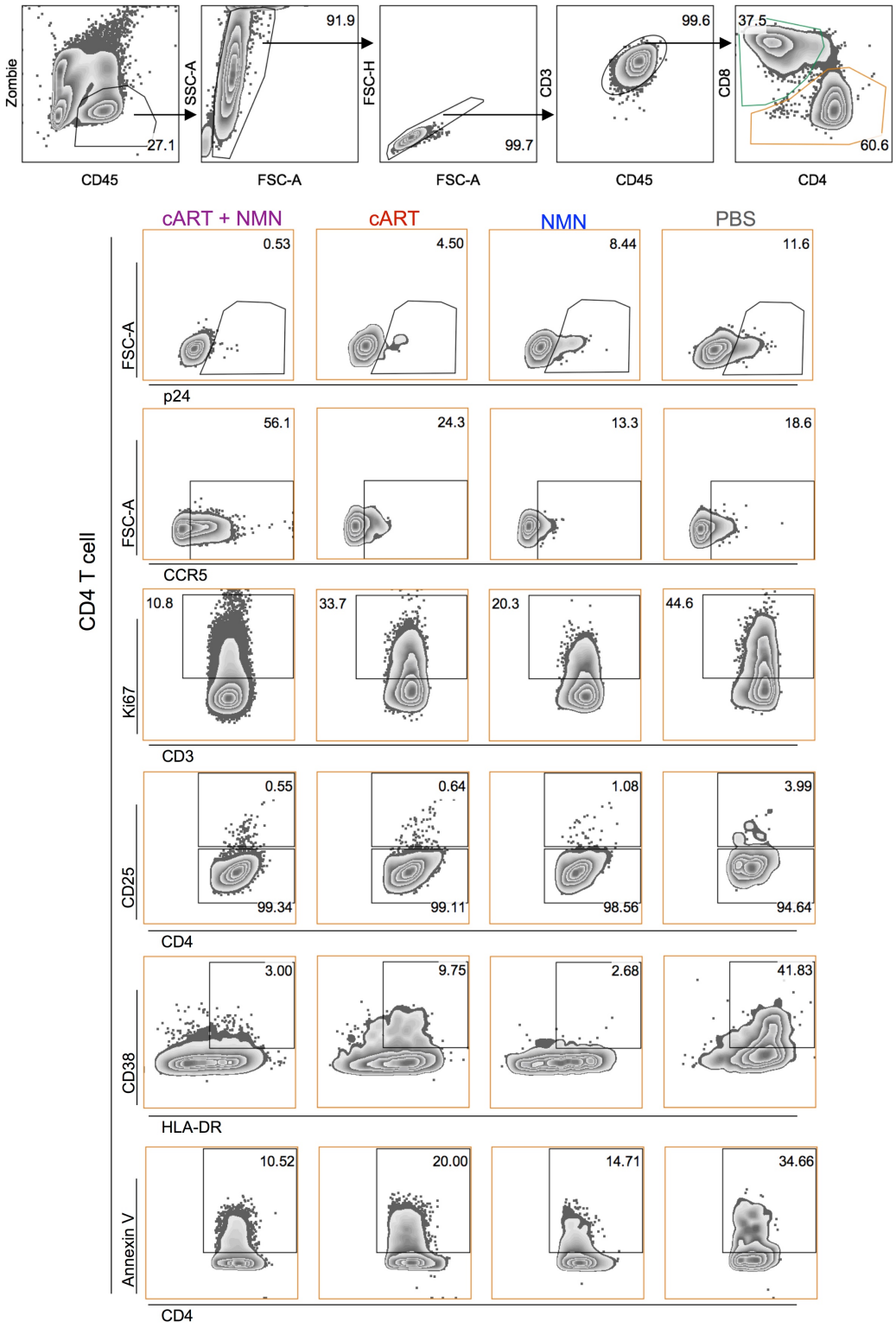


Supplementary Figure 12. The percentage of CD25$^+$, HLA-DR$^+$ and ki67$^+$ in p24$^+$ CD4$^+$ T cells under NMN treatment after HIV infection in the presence of EFV. Related to Figure 5.

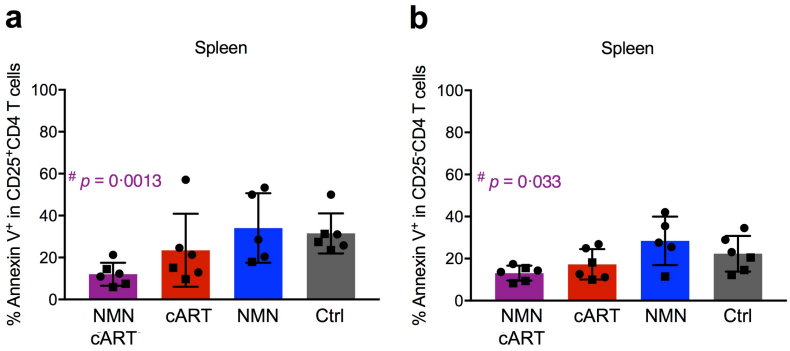
Primary CD4$^+$ T cells were isolated from PBMCs of 3 independent healthy donors and infected with live HIV-1_{JRFL} virus (2 ng p24 per 0·1 million cells) or mock in one experiment. At 24 hours post-infection, cells were treated without or with 10 mM NMN in the presence of 10 nM EFV and 10 U/mL IL-2. On Day 7 post-infection, cells were harvested for intracellular p24 staining and FACS analysis on CD25, HLA-DR, and ki67 expression. The representative plots **(a)** and the percentage **(b)** of CD25$^+$, HLA-DR$^+$ and ki67$^+$ in p24$^+$CD4$^+$ T cells were displayed. Data represent Mean. Each dot represents one independent individual.



Supplementary Figure 13. Gating strategy on human immune cells from peripheral blood cells in NMN-treated HIV-infected huPBL mice. Related to Figure 6.
Gating strategy on $CD4^+$ or $CD8^+$ T cells from $CD45^+$ cells and $CCR5^+CD4^+$ cells from peripheral blood cells of NMN-treated HIV-infected huPBL mice was displayed. The orange frame represents $CD4^+$ T cells.

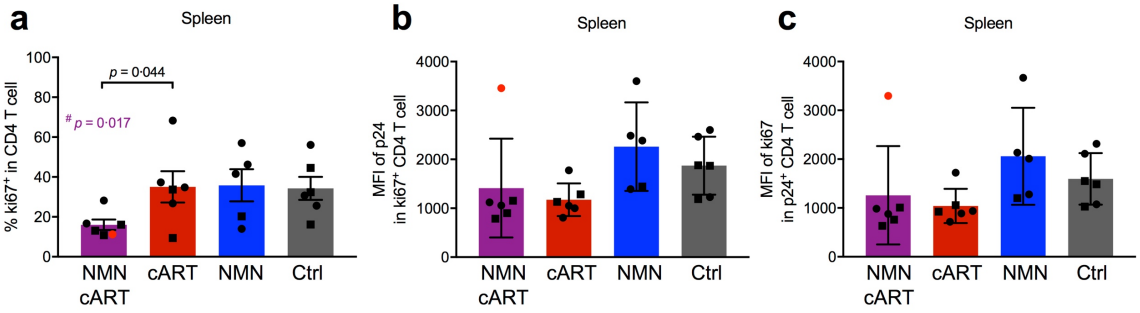


Supplementary Figure 14. Gating strategy on human immune cells from splenocytes in NMN-treated HIV-infected huPBL mice. Related to Figure 6.
Gating strategies on $CD4^+$ or $CD8^+$ T cells from $CD45^+$ cells, $p24^+CD4^+$ T cells, $CCR5^+CD4^+$ T cells, $ki67^+CD4^+$ T cells, $CD25^+CD4^+$ T cells $HLA\text{-}DR^+CD38^+CD4^+$ T cells and Annexin V^+CD4^+ T cells from splenocytes of NMN-treated HIV-infected huPBL mice were displayed. The orange frame represents $CD4^+$ T cells.



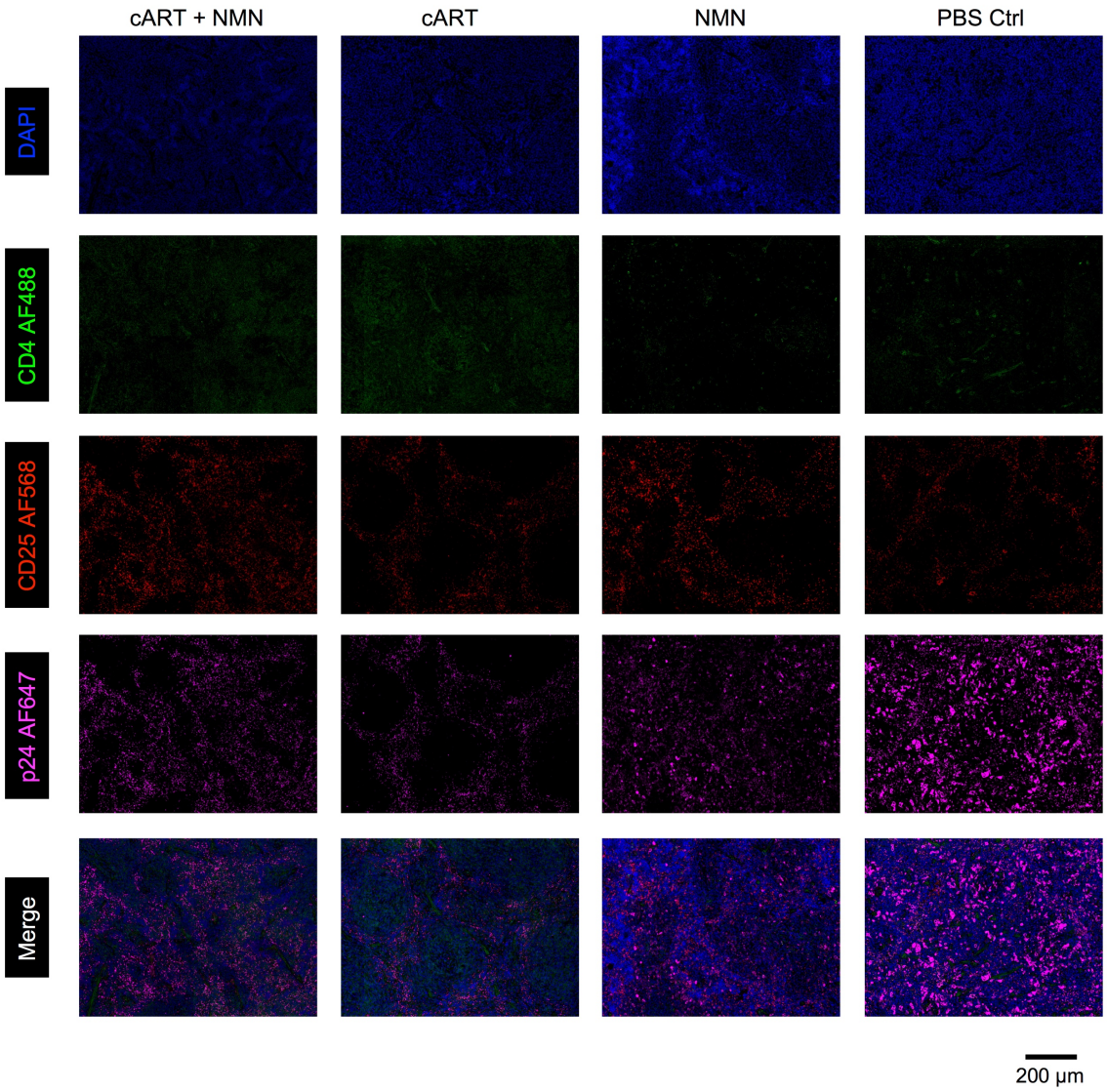
Supplementary Figure 15. NMN treatment plus cART did not selectively reduce apoptotic cells in either $CD25^+$ or $CD25^-$ $CD4^+$ T cells in the HIV-infected huPBL mouse model as compared to cART alone group. Related to Figure 6.

In HIV-infected huPBL mouse model, the percentage of Annexin V^+ cells in $CD25^+$ **(a)** or $CD25^-$ **(b)** $CD4^+$ T cells from splenocytes (Day 28 post-infection) was compared among groups. Data represent Mean ± SD; data passed normality test, and statistics were calculated based on unpaired Student's t-test. # represents the significant difference between experimental groups and the control group, and the corresponding *p* value was reported in the corresponding group colour (cART-plus-NMN group in purple). Each dot represents one individual mouse. Circles show mice from Batch 1, whereas rectangles show mice from Batch 2.



Supplementary Figure 16. NMN treatment plus cART reduces proliferating CD4$^+$ T cells in HIV-infected huPBL mouse model. Related to Figure 6.

In HIV-infected huPBL mouse model, the percentage of ki67$^+$ CD4$^+$ T cells **(a)**, MFI of p24 in ki67$^+$ CD4$^+$ T cells **(b)**, and MFI of ki67 in p24$^+$ CD4$^+$ T cells **(c)** from splenocytes (Day 28 post-infection) were compared among groups. Data represent Mean ± SD; data passed normality test, and statistics were calculated based on unpaired Student's t-test. # represents the significant difference between experimental groups and the control group, and the corresponding *p* value was reported in the corresponding group colour (cART group in red, while cART-plus-NMN group in purple). * represents the significant difference between cART group and cART-plus-NMN group, and the corresponding *p* value was reported in black colour. Two batches of mice were conducted in this experiment. Each dot represents one individual mouse. Circles show mice from Batch 1, whereas rectangles show mice from Batch 2. Note: The red dot in the cART-plus-NMN group was the individual which exclusively acquired a high MFI level of p24 in ki67$^+$ CD4$^+$ T cells or ki67 in p24$^+$ CD4$^+$ T cells in this FACS staining panel.



Supplementary Figure 17. Representative images of spleen sections from HIV-infected huPBL mice receiving cART and/or NMN. Related to Figure 6.
In HIV-infected huPBL mouse model, spleen tissues were collected on Day 28 post-infection when sacrificed. After immunohistochemistry (IHC) staining on tissue sections from spleen, IHC slides were scanned via PerkinElmer Vectra Polaris™ Automated Quantitative Pathology Imaging System and analysed by Inform Software. Representative images were displayed.