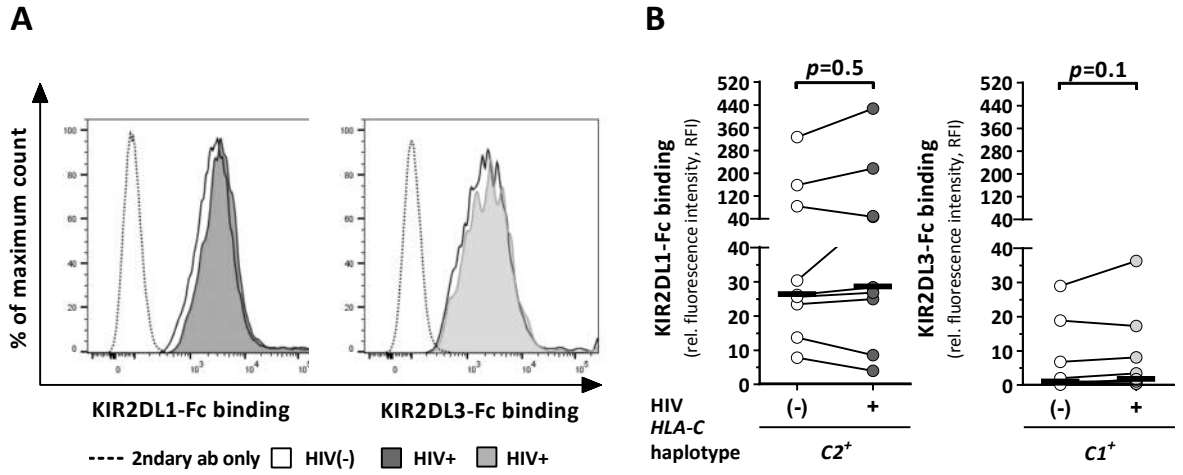

Figure S1. ***In vitro*** **infection with NL4-3 does not alter KIR2DL binding to infected CD4$^+$ T cells. Related to Figure 2.** **(A)** Representative histograms of KIR2DL1 (left panel) and KIR2DL3 binding (right panel) to uninfected CD4$^+$ T cells and cells infected with NL4-3 measured by flow cytometry. **(B)** Scatter plots display KIR2DL1 (left panel) and KIR2DL3 binding (right panel) to uninfected CD4$^+$ T cells and cells infected with NL4-3. Uninfected cells are displayed as clear circles; infected cells are either displayed as dark grey circles (KIR2DL1-Fc) or light grey circles (KIR2DL3-Fc). KIR binding is displayed only for donors expressing the cognate HLA-C ligand (C2$^+$: n=9; C1$^+$: n=9) and as relative median fluorescence intensity (RFI= [MFI (KIR-Fc+αIgG-PE)/MFI (αIgG-PE alone)]-1). Black bars represent the median. Statistical analysis was performed using Wilcoxon matched-pairs signed rank test.

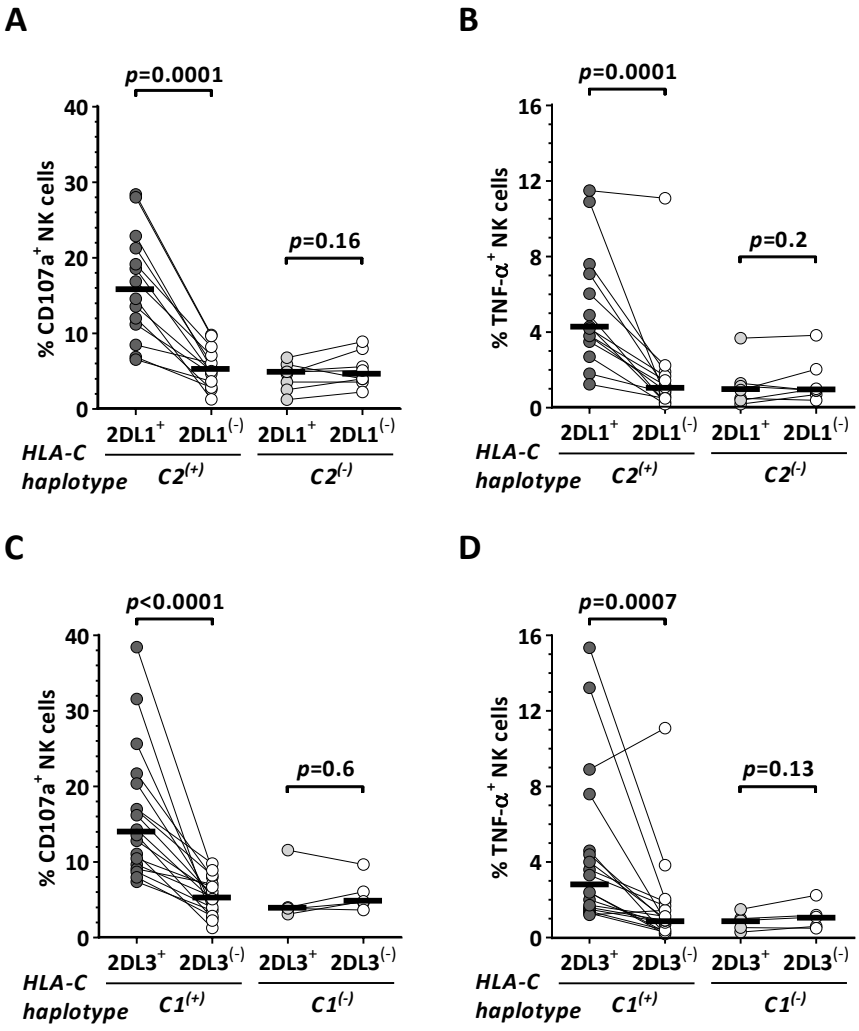

Figure S2. Licensing of KIR2DL$^+$ NK cells. Related Figure 3.
The figure shows the ability of HLA-C-licensed and un-licensed NK cells to respond to the MHC-class I devoid target cell line 721.221. Assessment of HLA-C-mediated licensing of NK cells was determined by frequency of CD107a expression **(A/C)** and production of TNF-α **(B/D)** using flow cytometry (n=23). Scatter plots display the frequency of CD107a$^+$ and TNF-α-producing cells among KIR2DL1$^+$ and KIR2DL1$^{(-)}$ **(A/B)** as well as KIR2DL3$^+$ and KIR2DL3$^{(-)}$ **(C/D)** stratified by the underlying HLA-C group haplotype. Respective NK-cell subsets were single-positive for the stated KIR2DL receptor additionally excluding NK cells co-expressing KIR3DL1 and/or NKG2A or lack all measured inhibitory receptors. Black bars represent the median. Wilcoxon matched-pairs signed rank test was used for statistical analysis of the data.

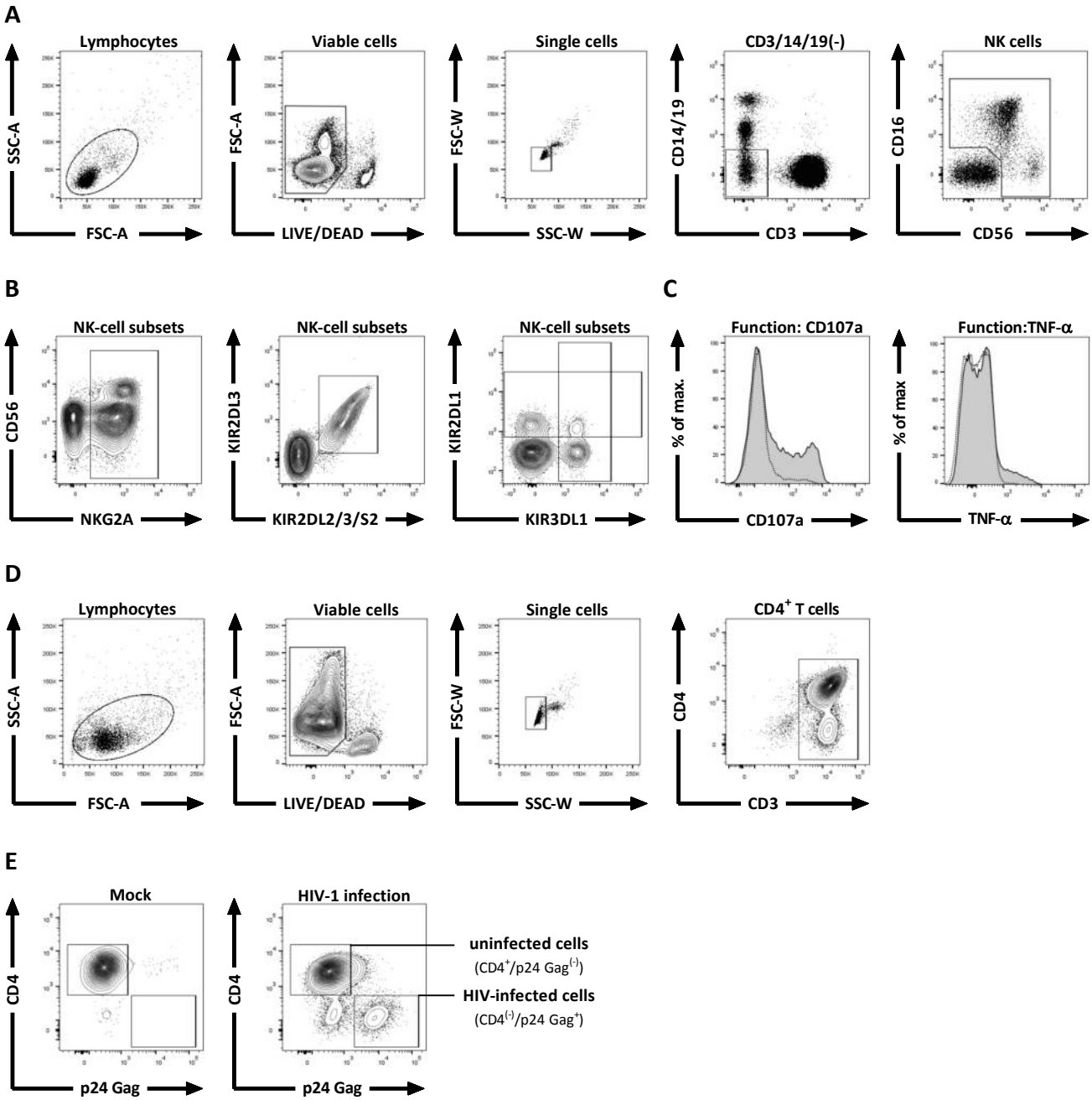

Figure S3. Gating strategies of flow cytometric analyses. Related to Figures 1-4.
Representative dot plots displaying the gating strategy after flow cytometric acquisition of lymphocytes. **(A)** Gating strategy to identify NK cells: After acquisition of PBMC lymphocytes were defined by forward (FSC-A) and sideward (SSC-A) scatter. Viable cells were identified by LIVE/DEAD blue. Doublets were excluded by forward (FSC-W) and sideward (SSC-W) scatter. Single, viable NK cells were then defined as $CD3^-/CD14^-/CD19^-$ $CD16^+$ or $CD56^+$ cells. **(B)** Identification of NK-cell subsets was conducted by using surface markers for NKG2A, KIR2DL1, KIR3DL1, KIR2DL3 and KIR2DL2/3/S2. **(C)** Functional assessment of NK cells was performed using CD107a expression and intracellular detection of TNF-α. Histograms display the fluorescence intensity of the respective marker in NK cells in the absence (tinted line, clear) and presence (grey, solid line) of MHC class I-devoid cell line 721.221. **(D)** For the assessment of HLA class I expression and KIR binding $CD4^+$ T cells were identified as follows: Enriched viable single $CD4^+$ T cells were identified by forward (FSC-A) and sideward (SSC-A) scatter, LIVE/DEAD blue, forward (FSC-W) and sideward (SSC-W) and expression of CD3. **(E)** Left panel shows mock-infected $CD4^+$ T cells as staining control for intracellular detection of p24 Gag. The right panel displays $CD4^+$ T cells after infection with HIV-1. Uninfected cells were defined as $CD4^+$ and p24 $Gag^{(-)}$ T cells, infected cells were determined based on the downregulation of CD4 and the expression of p24 Gag.

Table S1. *HLA class I* genotypes of enrolled subjects. Related to STAR Methods.

Subject-ID	*HLA-A*		*HLA-B*		*HLA-C*		*Bw4/6*[(+) a]	*HLA-C haplotype*[b]	Experiments performed with [c]
	A1	*A2*	*B1*	*B2*	*C1*	*C2*			
BC150609A	02:01	03:02	13:02	44:02	05:01	06:02	*Bw4*	*2/2*	HLA/KIR-Fc/Function
BC150609B	24:02	29:02	15:01	44:02	03:03	07:04	*Bw4*	*1/1*	HLA/KIR-Fc/Function
BC150609C	02:05	31:01	38:01	44:03	04:01	12:03	*Bw4*	*1/2*	HLA/KIR-Fc/Function
BC150526A	02:01	26:01	13:02	38:01	06:02	12:03	*Bw4*	*1/2*	HLA/KIR-Fc/Function
BC150526B	02:24	03:01	07:02	44:02	05:01	07:02	*Bw4*	*1/2*	HLA/KIR-Fc/ Function
BC150526C	01:01	01:01	08:01	08:01	07:01	07:01	*Bw6*	*1/1*	HLA/KIR-Fc/ Function
BC150623A	03:01	11:01	14:01	14:02	08:02	08:02	*Bw6*	*1/1*	HLA/KIR-Fc/ Function
BC150623B	02:01	02:01	08:01	18:01	07:01	07:01	*Bw6*	*1/1*	HLA/KIR-Fc/Function
BC150623C	03:01	03:01	07:02	55:01	07:02	07:02	*Bw6*	*1/1*	HLA/KIR-Fc/Function
BC160726B	01:01	24:02	14:02	35:02	04:01	08:02	*Bw6*	*1/2*	HLA/KIR-Fc/Function
BC160727A	01:01	02:01	27:05	44:03	01:02	16:01	*Bw4*	*1/1*	HLA/KIR-Fc/Function
BC160727B	02:01	02:06	07:02	44:02	05:01	07:02	*Bw4*	*1/2*	HLA/KIR-Fc/Function
BC170228A	02:01	03:01	40:01	51:01	03:04	14:02	*Bw4*	*1/1*	Function
BC170228B	24:02	31:01	07:02	51:01	07:02	15:02	*Bw4*	*1/2*	Function
BC170302A	02:01	02:01	44:02	51:07	05:01	14:02	*Bw4*	*1/2*	Function
BC170302B	02:01	24:02	40:01	51:01	03:04	04:01	*Bw4*	*1/2*	Function
BC170314A	31:01	68:01	40:01	57:01	03:04	07:01	*Bw4*	*1/1*	Function
BC170314B	02:01	02:05	39:01	58:01	07:01	07:02	*Bw4*	*1/1*	Function
BC170316A	03:01	11:01	07:02	35:01	04:01	07:02	*Bw6*	*1/2*	Function
BC170316B	24:02	32:01	07:02	08:01	07:01	07:02	*Bw4*	*1/1*	Function
BC170330A	02:01	03:01	44:02	55:01	03:03	05:01	*Bw4*	*1/2*	KIR-Fc
BC170330B	01:01	68:01	07:02	51:01	07:02	14:02	*Bw4*	*1/1*	KIR-Fc
HC164	02:01	03:01	07:02	15:01	03:04	07:02	*Bw6*	*1/1*	HLA/KIR-Fc
HC169	03:01	24:02	15:22	35:03	03:03	12:03	*Bw4*	*1/1*	HLA/KIR-Fc
HC184	02:01	02:01	35:03	40:02	02:02	12:03	*Bw6*	*1/2*	HLA/KIR-Fc
HC118	01:01	11:01	56:01	57:01	01:02	06:02	*Bw4*	*1/2*	HLA
HC190	02:01	24:02	13:02	27:05	02:02	06:02	*Bw4*	*2/2*	HLA
HC198	02:01	03:01	07:02	83:01	05:01	07:02	*Bw6*	*1/2*	HLA
HC028	24:02	26:01	35:01	44:02	04:01	05:09	*Bw4*	*2/2*	HLA/KIR-Fc
HC101	02:01	02:01	18:01	39:01	05:01	12:03	*Bw6*	*1/2*	HLA/KIR-Fc/Function
HC103	03:01	03:01	07:02	35:01	04:01	07:02	*Bw6*	*1/2*	HLA/VIA
HC104	03:01	31:01	13:02	18:01	06:02	07:01	*Bw4*	*1/2*	VIA
HC117	32:01	68:01	38:01	44:02	12:03	16:04	*Bw4*	*1/1*	HLA/KIR-Fc/Function
HC154	02:01	68:01	07:02	37:01	06:02	07:02	*Bw4*	*1/2*	HLA/KIR-Fc/Function
HC110	02:01	31:01	35:02	51:01	04:01	14:02	*Bw4*	*1/2*	HLA/KIR-Fc
HC195	01:01	02:01	18:01	57:01	06:02	07:01	*Bw4*	*1/2*	HLA/KIR-Fc
422548	02:01	02:01	40:01	51:01	03:04	14:02	*Bw4*	*1/1*	HLA/KIR-Fc/Function
424429	02:01	03:01	07:02	27:05	01:02	07:02	*Bw4*	*1/1*	HLA/KIR-Fc
447537	02:01	03:01	07:02	07:02	07:02	07:02	*Bw6*	*1/1*	HLA/KIR-Fc/Function
811054	02:01	32:01	07:02	07:05	07:02	15:05	*Bw6*	*1/2*	HLA/KIR-Fc
470384	01:01	02:01	07:05	44:02	05:01	15:05	*Bw4*	*2/2*	HLA/KIR-Fc
494230	01:01	80:01	08:01	15:03	02:10	07:01	*Bw6*	*1/2*	Function
IGTB0085		68:01	14:01	44:03	08:02	16:01	*Bw4*	*1/1*	Function
IGTB0162		33:01	14:02	38:01	08:02	12:03	*Bw4*	*1/1*	Function
IGTB0225		68:01	27:05	57:01	02:02	06:02	*Bw4*	*2/2*	Function
IGTB0302	23:01	74:00	15:03	15:03	02:10	02:10	*Bw6*	*2/2*	Function
IGTB0330	02:01	03:01	07:02	15:01	03:04	07:02	*Bw6*	*1/1*	Function
IGTB0520	11:01	26:01	08:01	15:08	03:04	07:02	*Bw6*	*1/1*	Function
IGTB0514		24:02	08:01	44:03	07:01	16:01	*Bw4*	*1/1*	Function
IGTB0741		24:02	13:01	39:06	03:04	07:02	*Bw4*	*1/1*	Function
IGTB0848		23:01	35:03	49:01	03:02	07:01	*Bw4*	*1/1*	Function
IGTB0884		24:02	15:01	51:01	03:04	15:09	*Bw4*	*1/2*	Function
120508	02:07	30:01	13:02	40:01	06:02	15:02	*Bw4*	*2/2*	HLA/KIR-Fc/Function
339477	02:01	11:01	14:01	27:02	02:02	08:02	*Bw4*	*1/2*	Function
902192	02:05	68:02	14:02	50:01	06:02	08:02	*Bw6*	*1/2*	Function
820666	02:01	11:01	15:03	44:02	05:01	16:01	*Bw4*	*1/2*	Function
963465	03:01	24:02	15:03	44:02	02:10	05:01	*Bw4*	*2/2*	Function
814129	11:01	11:02	15:12	51:01	03:03	14:02	*Bw4*	*1/1*	Function
736511	02:01	03:01	18:01	35:03	04:01	05:01	*Bw6*	*2/2*	HLA/KIR-Fc
160961	03:01	03:01	18:01	18:01	05:01	12:03	*Bw6*	*1/2*	HLA/KIR-Fc
773092	11:01	25:01	18:01	35:01	04:01	07:01	*Bw6*	*1/2*	Function
427341	02:01	03:01	35:01	44:02	04:01	05:01	*Bw4*	*2/2*	HLA/KIR-Fc
457386	26:01	31:01	35:01	38:01	04:01	12:03	*Bw4*	*1/2*	Function

991589	02:01	31:01	35:02	44:02	04:01	05:01	*Bw4*	*2/2*	HLA/KIR-Fc
522458	03:01	69:01	38:01	55:01	01:02	12:03	*Bw4*	*1/1*	Function
334026	02:01	32:01	40:01	44:03	03:04	16:01	*Bw4*	*1/1*	HLA/KIR-Fc
290892	11:01	11:02	40:01	46:01	01:02	07:02	*Bw6*	*1/1*	HLA/KIR-Fc
205460	01:01	03:01	44:02	52:01	05:01	12:02	*Bw4*	*1/2*	HLA/KIR-Fc/Function
453548	02:01	03:01	44:02	51:01	05:01	15:02	*Bw4*	*2/2*	Function
305415	02:01	11:01	44:03	51:01	07:01	14:02	*Bw4*	*1/1*	HLA/KIR-Fc/Function
471607	02:01	11:01	44:02	57:01	05:01	06:02	*Bw4*	*2/2*	HLA/KIR-Fc
653425	01:01	30:01	51:01	57:01	06:02	14:02	*Bw4*	*1/2*	Function

a) *Bw4*: Carrier of at least one HLA-B molecule with Bw4 motif; *Bw6*: Lack of Bw4 motif in both HLA-B molecules.
b) Haplotype based on HLA-C group of the two HLA-C alleles.
c) HLA: HLA-C expression levels; KIR-Fc: Assessment of KIR binding; Function: Assessment of NK-cell function and NK-cell-mediated inhibition of HIV-1 replication after exposure to 721.221 cells or HIV-infected $CD4^+$ T cells.

Table S2. Antibodies and flow cytometry specifications. Related to STAR Methods.

Antibody	Clone	Conjugate [a]	Vendor	Laser excitation (nm) [b]	Filter (LP, BP) [c]	Experiments [d]
α-human CD3	UCHT1	BV510	Biolegend	405	505, 525/50	HLA/KIR-Fc
α-human CD3	UCHT1	PE-Cf594	BD Bioscience	561	600, 610/20	Sorting/Function
α-human CD3	UCHT1	PerCP-Cy5.5	Biolegend	561	685, 710/40	Function
α-human CD4	RPA-T4	APC	BD Bioscience	640	670/30	HLA/KIR-Fc
α-human CD16	EG8	BV785	Biolegend	405	750, 780/60	Purity/Sorting/Function
α-human CD56	HCD56	BUV395	BD Bioscience	355	379/28	Purity/Sorting/Function
α-human CD8	HIT8a	FITC	BD Bioscience	488	505,525/50	Purity
α-human CD14	HCD14	APC-Cy7	Biolegend	640	750, 780/60	Sorting/Function
α-human CD14	HCD14	PerCP-Cy5.5	Biolegend	640	685, 710/40	Function
α-human CD19	HIB19	APC-Cy7	Biolegend	640	750, 780/60	Sorting/Function
α-human CD19	HIB19	PerCP-Cy5.5	Biolegend	640	685, 710/40	Function
α-human KIR2DL1/S5	143211	FITC	R&D Systems	488	505,525/50	Sorting/Function
α-human KIR2DL1/S5	143211	-	R&D Systems	-	-	Blocking
α-human KIR2DL3	180701	APC	R&D Systems	633	670/30	Sorting/Function
α-human KIR2DL3	180701	-	R&D Systems	-	-	Blocking
α-human KIR2DL2/3/S2	DX27	PE	Biolegend	561	582/15	Function
α-human KIR3DL1	DX9	AF700	Biolegend	633	685, 730/45	Function
α -human NKG2A	Z199	PE-Cy7	BeckmanCoulter	561	750, 780/60	Function
α-human CD107a	H4A3	BV421	Biolegend	405	450/50	Function
α-human CD107a	H4A3	BV510	Biolegend	405	505, 525/50	Function
α-human TNF-α	MAb11	BV650	Biolegend	405	635, 675/50	Function
α-human HLA-C	DT9	-	Merck-Millipore	-	582/15	HLA
α-mouse IgG	poly	PE	Sigma	561	582/15	HLA
KIR2DL1-IgG_1	-	-	R&D Systems	-	-	KIR-Fc
KIR2DL3-IgG_1	-	-	R&D Systems	-	-	KIR-Fc
α-human IgG	poly	R-PE	Invitrogen	561	582/15	KIR-Fc
α-HIV-1 core antigen	KC57	FITC	BeckmanCoulter	488	505,525/50	HLA/KIR-Fc
α-human CD45RO	UCHL1	-	Biolegend	-	-	Function
LIVE/DEAD Blue [e]	-	-	Invitrogen	355	410, 450/50	All experiments

a) BV: Brilliant Violet; BUV: Brilliant Ultraviolet; APC: Allophycocyanin; FITC: Fluorescein isothiocyanate; PE: Phycoerythrin; AF: AlexaFluor

b) Laser power, LSR Fortessa/Sorp ARIA II: 355nm: 60mW/100mW; 405nm: 100mW; 488nm: 50mW/200mW; 561nm: 50mW/150mW; 640nm: 40mW/140mW

c) LP = long pass filter, BP = band pass filter.

d) HLA: HLA-C Expression levels; KIR-Fc: Assessment of KIR binding; Function: Assessment of NK-cell function and NK-cell-mediated inhibition of HIV-1 replication after exposure to 721.221 cells or HIV-infected $CD4^+$ T cells.

e) Amine-reactive dye