FIG. S1. Identification of optimal CTL epitopes.
The 11-mer overlapping peptide-specific bulk CD8^{+} T cells were stimulated with truncated peptide-prepulsed C1R or .221 cells expressing each HLA allele. **(A)** IFN-γ production from the bulk CD8^{+} T cells was detected by using the ICS assay. Determination of an optimal epitope was performed at a 100 nM or 1000 nM peptide concentration. **(B)** When the same level of response was seen at 100 nM or 1000 nM, the assay was performed again at concentrations from 0.1 to 1000 nM. The HLA restriction of epitope-specific CD8^{+} T cell responses is indicated in parentheses in "a" and "b".
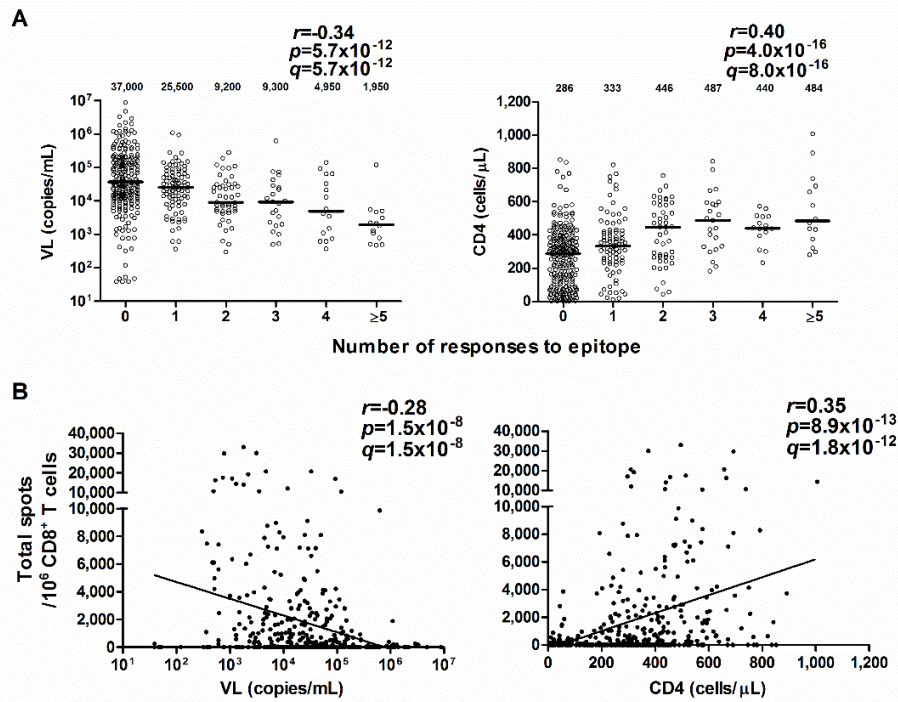
1

FIG. S2. Correlation between multiple CD8$^+$ T cell responses to 13 epitopes and pVL or CD4 counts in 393 chronically HIV-1-infected Japanese individuals.
Epitope-specific CD8$^+$ T cell responses in 393 Japanese individuals were analyzed by using the ELISPOT assay. **(A)** Correlation between the breadth of 13 epitope-specific CD8$^+$ T cell responses and VL or CD4 counts. The values and the lines in each figure represent the medians of VL or CD4 counts. Statistical analysis was performed by use of the Pearson's correlation coefficient test. **(B)** Correlation between the total magnitude of these responses and pVL or CD4 counts. Correlation coefficients (r) and p values were determined by performing the Spearman rank correlation test. The line is the regression line. Each dot represents 1 individual. Multiple tests were performed by using the *q*-value, a measure of significance in terms of the false discovery rate [Storey JD, Tibshirani R. 2003. Proc Natl Acad Sci U S A]. A significance threshold of *q* < 0.2 was employed.
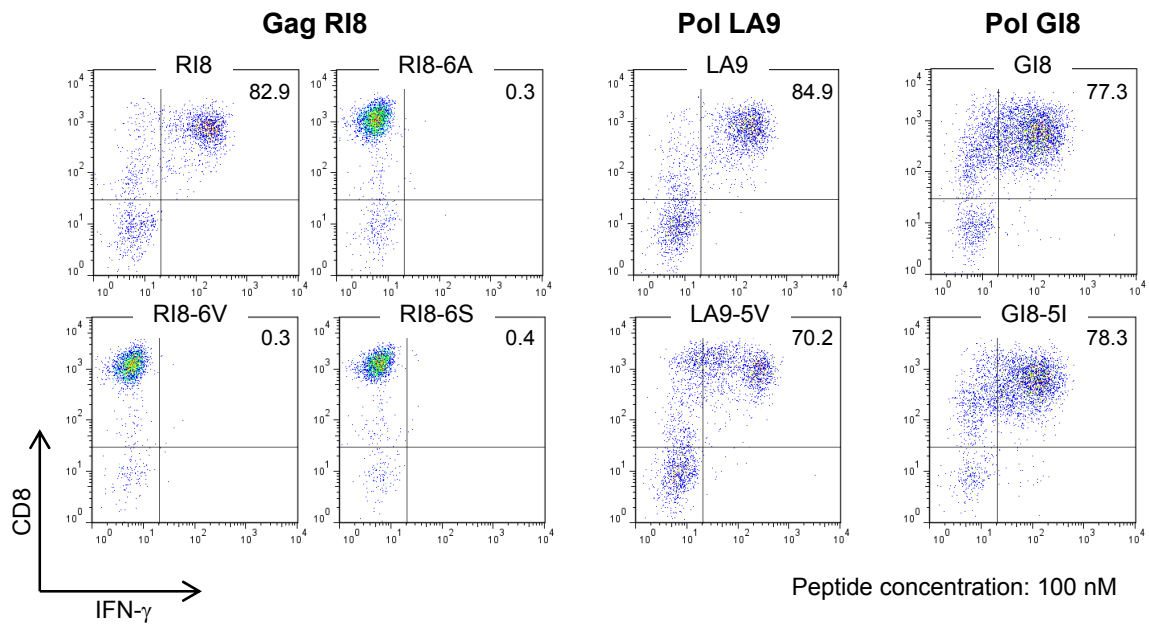
FIG. S3. Recognition of mutant peptides or wild-type (WT) peptide by epitope-specific CD8+ T cells.

The epitope-specific CTL clones were stimulated with mutant or WT peptide-prepulsed C1R cells expressing the corresponding HLA allele, and then IFN-γ production from these CTL clones was detected by performing the ICS assay. These figures represent the raw data for IFN-γ production from epitope-specific CTL clones at a peptide concentration of 100 nM shown in Fig. 5B. The percentages of IFN-γ-producing cells among CD8+ T cells are shown in each figure.

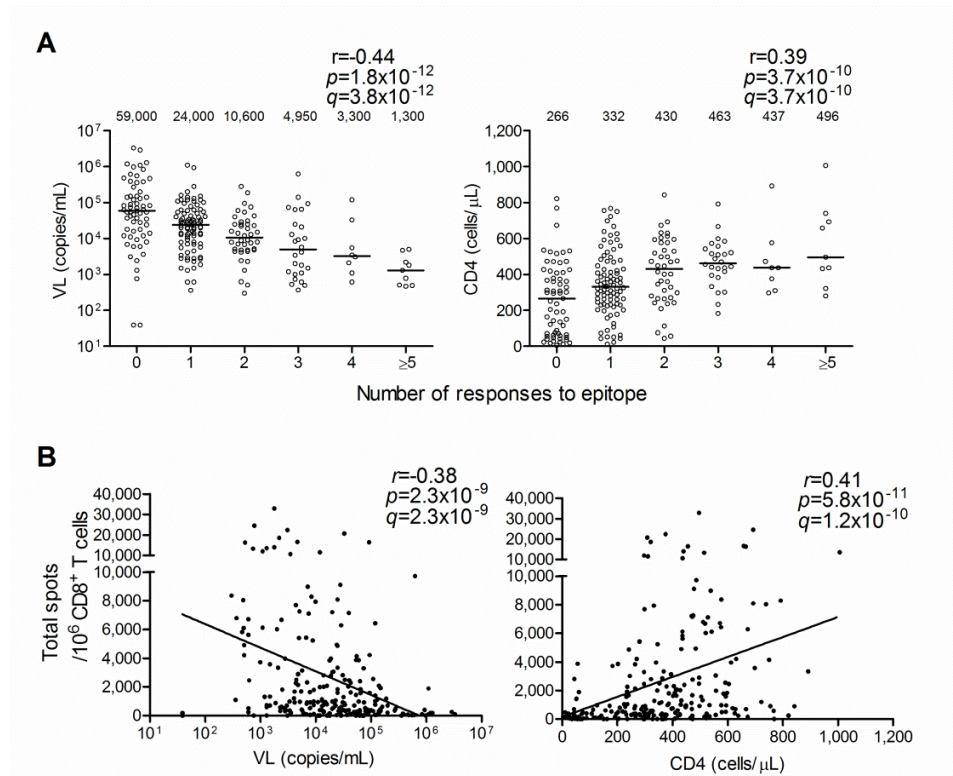**FIG. S4. Correlation between multiple CD8^{+} T cell responses to 12 conserved and cross-reactive epitopes and pVL or CD4 counts in chronically HIV-1-infected Japanese individuals.**

Epitope-specific CD8^{+} T cell responses at a peptide concentration of 100 nM were analyzed by using the ELISPOT assay. **(A)** Correlation between the breadth of 12 conserved and cross-reactive epitope-specific CD8^{+} T cell responses and pVL or CD4 counts in Japanese individuals carrying at least one of the restricting HLA alleles (n = 235). The values and the lines in each figure represent medians of pVL and CD4 counts (left and right graphs, respectively). Statistical analysis was performed by use of the Pearson's correlation coefficient test. **(B)** Correlation between the total magnitude of these responses and pVL or CD4 counts in the Japanese individuals. The lines are regression lines. Correlation coefficients (r) and p-values were determined by using the Spearman rank correlation test. Multiple tests were performed by using the q-value. A significance threshold of $q < 0.2$ was employed.

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TABLE S1. HLA alleles significantly correlated with low pVL and high CD4 counts in CD8+ T cell responder to each Nef, Gag or Pol peptide cocktail.

Cocktail	HLA	Frequency		pVL (copies/mL)		CD4 (cells/μL)		p value		q value	
		Responder	Non-responder	Responder	Non-responder	Responder	Non-responder	pVL	CD4	pVL	CD4
Nef G4	B*52:01	12	389	5250	25000	419	324	0.048	0.075	0.086	0.13
	C*03:04	17	384	8900	26000	324	325	0.004	0.467	0.0075	0.6
	C*12:02	12	389	5250	25000	419	324	0.048	0.075	0.086	0.13
Nef G5	B*40:06	14	387	6350	25000	429	321	0.012	0.08	0.022	0.14
Nef G6	A*11:01	12	389	6950	25000	384	321	0.045	0.055	0.081	0.098
	B*15:01	13	388	6000	25500	386	321	0.019	0.091	0.035	0.16
Nef G9	A*31:01	10	391	5500	26000	392	324	0.002	0.36	0.0038	0.49
Gag G9	A*24:02	62	339	16000	27000	381	315	0.028	0.012	0.051	0.022
	B*52:01	22	379	4450	27000	451	319	0.0003	0.002	0.00057	0.0038
	B*67:01	14	387	8650	25000	409	321	0.064	0.013	0.11	0.024
	C*07:02	27	374	10000	26500	387	319	0.012	0.009	0.022	0.017
	C*08:01	14	387	5400	26000	443	321	0.001	0.018	0.0019	0.033
	C*12:02	22	379	4450	27000	451	319	0.0003	0.002	0.00057	0.0038
Gag G10	B*52:01	10	391	4850	26000	493	322	0.001	0.079	0.0019	0.14
	C*12:02	10	391	4850	26000	493	322	0.001	0.079	0.0019	0.14
Gag G14	B*52:01	11	390	5600	25500	382	321	0.019	0.038	0.035	0.069
	C*12:02	11	390	5600	25500	382	321	0.019	0.038	0.035	0.069
Gag G15	C*03:04	13	388	7900	25000	414	323	0.009	0.068	0.017	0.12
Gag G16	A*24:02	33	368	7900	27000	378	321	0.001	0.058	0.0019	0.1
	B*52:01	31	370	5600	27000	432	320	0.0005	0.014	0.00094	0.026
	C*12:02	31	370	5600	27000	432	320	0.0005	0.014	0.00094	0.026
Gag G17	A*02:06	33	368	19000	25500	418	317	0.092	0.003	0.16	0.0056
	A*11:01	14	387	15500	25000	612	321	0.068	0.0002	0.12	0.00038
	A*24:02	42	359	10750	26000	365	319	0.028	0.018	0.051	0.033
	B*40:02	10	391	8400	25000	504	322	0.044	0.054	0.079	0.097
	B*52:01	20	381	5350	26000	470	321	0.005	0.004	0.0094	0.0075
	B*67:01	10	391	4500	25000	409	322	0.012	0.054	0.022	0.097
	C*07:02	21	380	4700	26000	427	320	0.005	0.004	0.0094	0.0075
	C*12:02	20	381	5350	26000	470	321	0.005	0.004	0.0094	0.0075
Gag G18	A*02:06	26	375	14650	26000	432	318	0.04	0.002	0.072	0.0038
	B*52:01	10	391	3550	25000	453	321	0.032	0.02	0.058	0.037
	C*12:02	10	391	3550	25000	453	321	0.032	0.02	0.058	0.037
Gag G20	A*11:01	10	391	13500	25000	464	321	0.09	0.003	0.15	0.0056
Gag G24	B*40:02	15	386	9300	26500	362	322	0.011	0.064	0.02	0.11
	C*03:04	14	387	11150	26000	404	322	0.014	0.04	0.026	0.072
Pol G4	B*52:01	13	388	7700	25000	469	321	0.051	0.002	0.091	0.0038
	C*12:02	13	388	7700	25000	469	321	0.051	0.002	0.091	0.0038
Pol G8	A*11:01	19	382	13000	25500	382	321	0.042	0.044	0.076	0.079
	C*04:01	11	390	7700	25500	443	321	0.033	0.005	0.06	0.0094
Pol G14	A*11:01	12	389	7600	25000	499	321	0.013	0.001	0.024	0.0019
	A*31:01	17	384	6000	26500	358	322	0.001	0.122	0.0019	0.2
	C*03:04	13	388	8000	25000	450	322	0.033	0.031	0.06	0.057
Pol G19	C*03:04	12	389	7950	26000	373	324	0.003	0.161	0.0056	0.25
Pol G22	A*02:06	47	354	14000	27000	386	314	0.015	0.01	0.028	0.019
	B*15:01	19	382	4400	26500	425	321	0.0003	0.004	0.00057	0.0075
	B*52:01	15	386	7700	26000	436	321	0.023	0.011	0.042	0.02
	C*03:04	17	384	9300	25500	450	322	0.048	0.044	0.086	0.079
	C*08:01	10	391	11250	25000	473	321	0.049	0.004	0.088	0.0075
	C*12:02	15	386	7700	26000	436	321	0.023	0.011	0.042	0.02
Pol G33	A*24:02	29	372	4400	27000	436	320	0.0002	0.004	0.00038	0.0075
	B*52:01	30	371	4400	27000	440	319	0.001	0.002	0.0019	0.0038
	C*12:02	30	371	4400	27000	440	319	0.001	0.002	0.0019	0.0038
Pol G34	A*11:01	14	387	8000	25000	576	321	0.064	0.0002	0.11	0.00038
Pol G38	B*52:01	14	387	5600	26000	451	321	0.005	0.053	0.0094	0.095
Pol G40	A*11:01	11	390	3000	26500	386	323	0.0002	0.111	0.00038	0.19
	B*40:06	24	377	5400	27000	383	322	0.001	0.232	0.0019	0.35
	C*08:01	26	375	7600	27000	383	322	0.002	0.178	0.0038	0.27
Pol G46	A*31:01	17	384	8000	27000	362	321	0.009	0.079	0.017	0.14
	B*40:02	41	360	14000	28000	368	319	0.016	0.009	0.03	0.017

We statistically analyzed differences in pVL or CD4 counts between responders to each cocktail in individuals carrying a given HLA and the other individuals by using the two-tailed Mann-Whitney's test. We then selected HLA alleles significantly associated with low pVL and high CD4 counts in the responders to each cocktail under the following two criteria; 1) HLA alleles associated with both low pVL and high CD4 counts (*p*-values in pVL and CD4 counts were less than 0.1 and 0.05, respectively, or less than 0.05 and 0.1, respectively) or those associated with low pVL ($p < 0.005$). 2) The frequency of responders is more than 2% (more than 9 out of 401 subjects). Multiple tests were performed by using the *q*-value, a measure of significance in terms of the false discovery rate [Storey JD, Tibshirani R. 2003. Proc Natl Acad Sci U S A]. A significance threshold of $q < 0.2$ was employed.

TABLE S2. Identification of CD8^{+} T cell responses to fifty-three 11-mer single peptides in 22 peptide cocktails by using ELISPOT assay or ICS assay.

Cocktail	Single peptide	Spots/10[6] CD8^{+} T cells in ELISPOT assay
Nef G4	Nef 32	310
Nef G5	Nef 41	8419
	Nef 42	9704
Nef G6	Nef 59	2115
Nef G9	Nef 88	533
	Nef 89	789
Gag G9	Gag 81	1466
	Gag 82	1442
	Gag 89	10613
	Gag 90	15000
Gag G14	Gag 134	323
	Gag 135	2507
	Gag 138	243
Gag G15	Gag 148	1806
Gag G17	Gag 162	7480
	Gag 163	214
	Gag 164	1196
	Gag 167	385
	Gag 168	3855
	Gag 169	337
	Gag 170	1292
Gag G18	Gag 175	1486
Gag G20	Gag 192	725
Gag G24	Gag 239	349
	Gag 240	411
Pol G8	Pol 73	2690
	Pol 74	234
Pol G14	Pol 131	9373
	Pol 132	8277
	Pol 134	980
	Pol 135	1220
	Pol 137	683
Pol G19	Pol 181	499
	Pol 185	265
	Pol 186	804
	Pol 189	748
	Pol 190	289
Pol G22	Pol 211	738
	Pol 212	443
Pol G38	Pol 371	6022
	Pol 372	5756
	Pol 376	200
Pol G40	Pol 391	1890
	Pol 392	3333
	Pol 400	1787

Cocktail	Single peptide	IFN-γ^{+} CD8^{+} T cells in ICS assay (%)
Gag G10	Gag 98	14.2
	Gag 99	6.2
	Gag 100	17.4
Gag G16	Gag 157	7.2
	Gag 158	5.3
Gag G18	Gag 171	14.6
Pol G33	Pol 326	43.2
	Pol 327	44.6

CD8^{+} T cell responses to fifty-three 11-mer overlapping peptides were detected by using ELISPOT assay or ICS assay. For the ICS assay, peptide cocktail-specific bulk T cells were stimulated with autologous EBV-transformed B cell lines pre-pulsed with 11-mer single peptides, and then IFN-γ production from the T cells was detected by using flow cytometry.

TABLE S3. HLA restriction of CTL responses to twenty-three 11-mer single peptides.

Cocktail	Single peptide	HLA restriction	IFN-γ⁺CD8⁺ T cells (%)	
			HLA⁺ ᵃ	HLA⁻ ᵇ
Nef G6	Nef 59	B*15:01	3.0	0.5
Gag G9	Gag 89	C*08:01	17.1	0.6
		B*67:01	31.4	0.4
	Gag 90	B*67:01	57.2	0.4
Gag G10	Gag 98	B*52:01	28.2	0.5
		C*12:02	1.0	
	Gag 99	B*52:01	15.7	1.2
		C*12:02	1.0	
	Gag 100	B*52:01	18.5	1.0
		C*12:02	1.0	
Gag G14	Gag 138	B*52:01	12.0	0.1
		C*12:02	0.4	
Gag G15	Gag 148	C*03:04	6.8	3.0
Gag G16	Gag 157	B*52:01	83.1	0.6
		C*12:02	0.6	
	Gag 158	B*52:01	77.0	1.6
		C*12:02	1.1	
Gag G17	Gag 164	B*67:01	4.3	0
	Gag 169	B*67:01	8.3	0
	Gag 170	A*02:06	4.2	0.3
Gag G18	Gag 171	A*02:06	12.3	0.1
Gag G24	Gag 239	B*40:02	6.5	1.3
	Gag 240	B*40:02	14.2	3.6
Pol G22	Pol 211	A*02:06	3.7	0.2
	Pol 212	A*02:06	4.8	0.1
Pol G33	Pol 326	B*52:01	48.5	0
		C*12:02	0.9	
	Pol 327	B*52:01	23.2	0.1
		C*12:02	0.2	
Pol G40	Pol 391	B*40:06	8.8	0.3
	Pol 392	B*40:06	34.9	3.6
	Pol 400	B*40:06	8.8	0.3

ᵃ C1R or .221 cells expressing corresponding HLA were used as stimulators in the ICS assay.

ᵇ C1R or .221 cells not expressing HLA were used as stimulators in the ICS assay.

HLA restrictions of CTL responses to 11-mer single peptide were determined by analyzing HLA restriction of the bulk CD8⁺ T cell response specific for each 11-mer peptide by the ICS assay using C1R or 721.221 transfectants expressing HLA alleles. The T cell responses to Gag 98/99/100/148/157/158 and Pol 326/327 single peptides were restricted by HLA-B*52:01, although HLA-B*52:01-C*12:02 completely forms a haplotype in Japanese.

TABLE S4. HLA restriction of CTL responses to the other single peptides.

Cocktail	Single peptide	HLA restriction	IFN-γ⁺ CD8⁺ T cells in ICS assay (%)
Nef G4	Nef 32	ND[a]	ND[a]
Nef G5	Nef 41	C*08:01	91.6
	Nef 42	C*08:01	84.2
Nef G9	Nef 88	B*40:02	2.5
	Nef 89	B*40:02	10.1
Gag G9	Gag 81	C*14:03	3.2
	Gag 82	C*14:03	16.0
Gag G14	Gag 134	B*15:01	42.3
	Gag 135	B*15:01	45.8
Gag G17	Gag 162	B*51:01	3.5
	Gag 163	ND[a]	ND[a]
	Gag 167	C*08:01	10.3
	Gag 168	C*08:01	7.1
Gag G18	Gag 175	ND[a]	ND[a]
Gag G20	Gag 192	B*15:01	6.6
Pol G8	Pol 73	B*15:01	5.4
	Pol 74	B*15:01	5.1
Pol G14	Pol 131	C*04:01	44.6
	Pol 132	C*04:01	40.3
	Pol 134	B*39:02	22.4
	Pol 135	B*39:02	27.6
	Pol 137	B*35:01	3.7
Pol G19	Pol 181	B*40:02	0.8
	Pol 185	A*02:06	1.2
	Pol 186	B*40:02	2.2
	Pol 189	B*40:02	2.6
	Pol 190	A*02:06	1.6
Pol G38	Pol 371	B*51:01	33.1
	Pol 372	B*51:01	23.0
	Pol 376	ND[a]	ND[a]

[a]ND: not detected

HLA restrictions of CTL responses to 11-mer single peptide were determined by analyzing HLA restriction of the bulk CD8⁺ T cell response specific for each 11-mer peptide by the ICS assay using C1R or 721.221 transfectants expressing HLA alleles.

TABLE S5. Associations of each HLA allele with mutations in 13 epitopes in chronically HIV-1-infected Japanese individuals

Epitope		1	2	3	4	5	6	7	8	9	10	11
Gag EM11 EGATPQDLNTM B*67:01[a]	Amino acid	E	G	A	T	P	Q	D	L	N	T	M
	p-value	1	1	1	1	1	1	1	1	1	1	1
	q-value	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864
Gag TL9 TPQDLNTML B*67:01[a]	Amino acid	T	P	Q	D	L	N	T	M	L		
	p-value	1	1	1	1	1	1	1	1	1		
	q-value	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864		
Gag MI8 MQMLKETI B*52:01[a]	Amino acid	M	Q	M	L	K	E	T	I			
	p-value	1	1	0.161473	1	1	0.775699	0.071162	1			
	q-value	0.996864	0.996864	0.897684	0.996864	0.996864	0.972235	0.810807	0.996864			
Gag QA11 QMLKETINEEA B*52:01[a]	Amino acid	Q	M	L	K	E	T	I	N	E	E	A
	p-value	1	0.161473	1	1	0.775699	0.071162	1	1	0.580277	1	1
	q-value	0.996864	0.897684	0.996864	0.996864	0.972235	0.810807	0.996864	0.996864	0.972235	0.996864	0.996864
Gag RI8 RMYSPTSI B*52:01[a]	Amino acid	R	M	Y	S	P	T	S	I			
	p-value	1	1	1	1	1	0.000171	0.558998	1			
	q-value	0.996864	0.996864	0.996864	0.996864	0.996864	0.046801	0.972235	0.996864			
Gag WV8 WMTETLLV B*52:01[a]	Amino acid	W	M	T	E	T	L	L	V			
	p-value	1	1	1	1	0.256614	1	1	1			
	q-value	0.996864	0.996864	0.996864	0.996864	0.939702	0.996864	0.996864	0.996864			
Gag NL9 NPDCKTILKAL B*67:01[a]	Amino acid	N	P	D	C	K	T	I	L	K	A	L
	p-value	1	1	1	1	1	1	1	1	1	1	1
	q-value	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864	0.996864
Gag AA9 ATLEEMMTA A*02:06[a]	Amino acid	A	T	L	E	E	M	M	T	A		
	p-value	0.197279	0.50022	1	1	1	1	1	0.248714	1		
	q-value	0.919283	0.972235	0.996864	0.996864	0.996864	0.996864	0.996864	0.933293	0.996864		
Pol SV9 SQIYAGIKV A*02:06[A]	Amino acid	S	Q	I	Y	A	G	I	K	V		
	p-value	1	1	1	1	0.025303	1	0.392286	0.010407	4.71E-11		
	q-value	0.995582	0.995582	0.995582	0.995582	0.714741	0.995582	0.942198	0.546553	1.1E-14		
Pol SI8 SQYALGII B*52:01[a]	Amino acid	S	Q	Y	A	L	G	I	I			
	p-value	1	1	1	1	1	1	1	0.18922			
	q-value	0.995604	0.995604	0.995604	0.995604	0.995604	0.995604	0.995604	0.919774			
Pol LA9 LEGKIILVA B*40:06[a]	Amino acid	L	E	G	K	I	I	L	V	A		
	p-value	1	1	1	1	0.192623	1	0.709803	1	1		
	q-value	0.995604	0.995604	0.995604	0.995604	0.919774	0.995604	0.943497	0.995604	0.995604		
Pol IT10 IEAEVIPAET B*40:06[a]	Amino acid	I	E	A	E	V	I	P	A	E	T	
	p-value	0.042556	1	1	1	1	1	0.165664	0.238844	1	1	
	q-value	0.792545	0.995604	0.995604	0.995604	0.995604	0.995604	0.919357	0.919774	0.995604	0.995604	
Pol GI8 GERIVDII B*40:02[a]	Amino acid	G	E	R	I	V	D	I	I			
	p-value	1	0.12533	1	0.315204	1	1	0.669875	0.301153			
	q-value	0.995582	0.86559	0.995582	0.933283	0.995582	0.995582	0.9431	0.931819			

[a] the HLA restriction of each epitope

The frequency of the mutation within each epitope between HLA[+] and HLA[-] individuals in 401 chronically HIV-1-infected Japanese individuals was statistically analyzed by using Fischer's extra test. Multiple tests were performed by using the *q*-value, a measure of significance in terms of the false discovery rate [Storey JD, Tibshirani R. 2003. Proc Natl Acad Sci U S A]. In the analyses identifying HLA-associated polymorphisms, a significance threshold of $q < 0.2$ was employed.

TABLE S6. Epitope sequences in the patients shown in FIG. 5C.

Gag RI8

	RMYSPTSI
KI-692	--------
KI-829	--------
KI-902	--------

Pol LA9

	LEGKIILVA
KI-756	---------
KI-763	---------
KI-912	----V----
KI-928	---------

Pol SV9

	SQIYAGIKV
KI-643	----S----
KI-763	----S----
KI-912	----P--R-
KI-926	---------

Pol GI8

	GERIVDII
KI-472	--------
KI-763	----I---
KI-909	--------