Figure S1

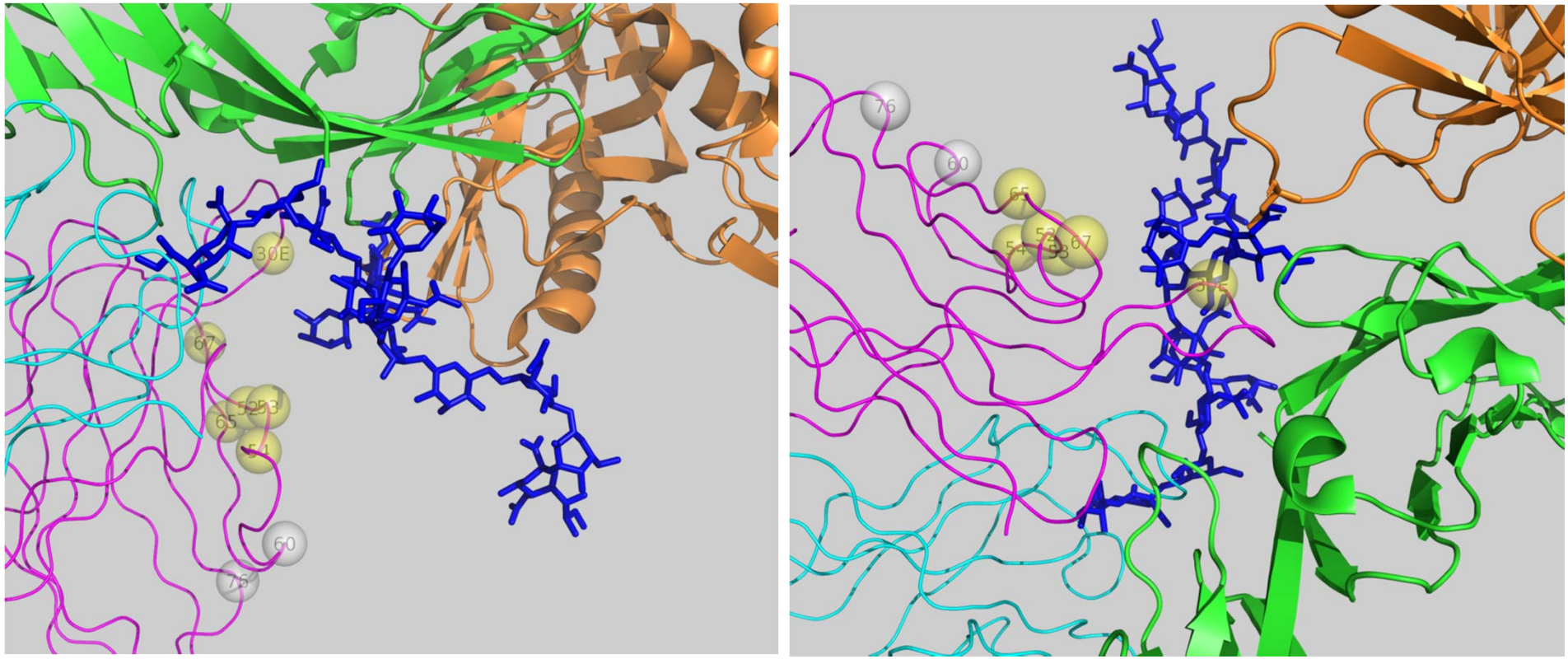

Figure S2

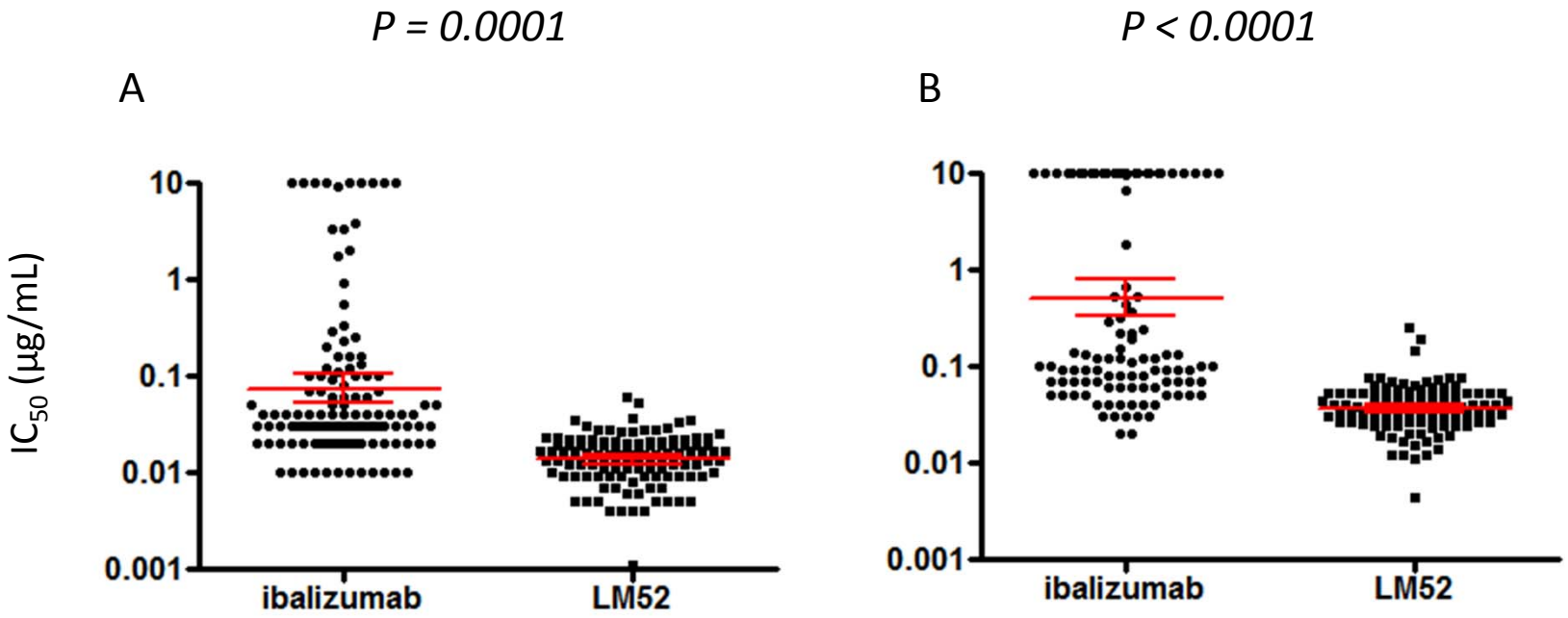

Figure S3

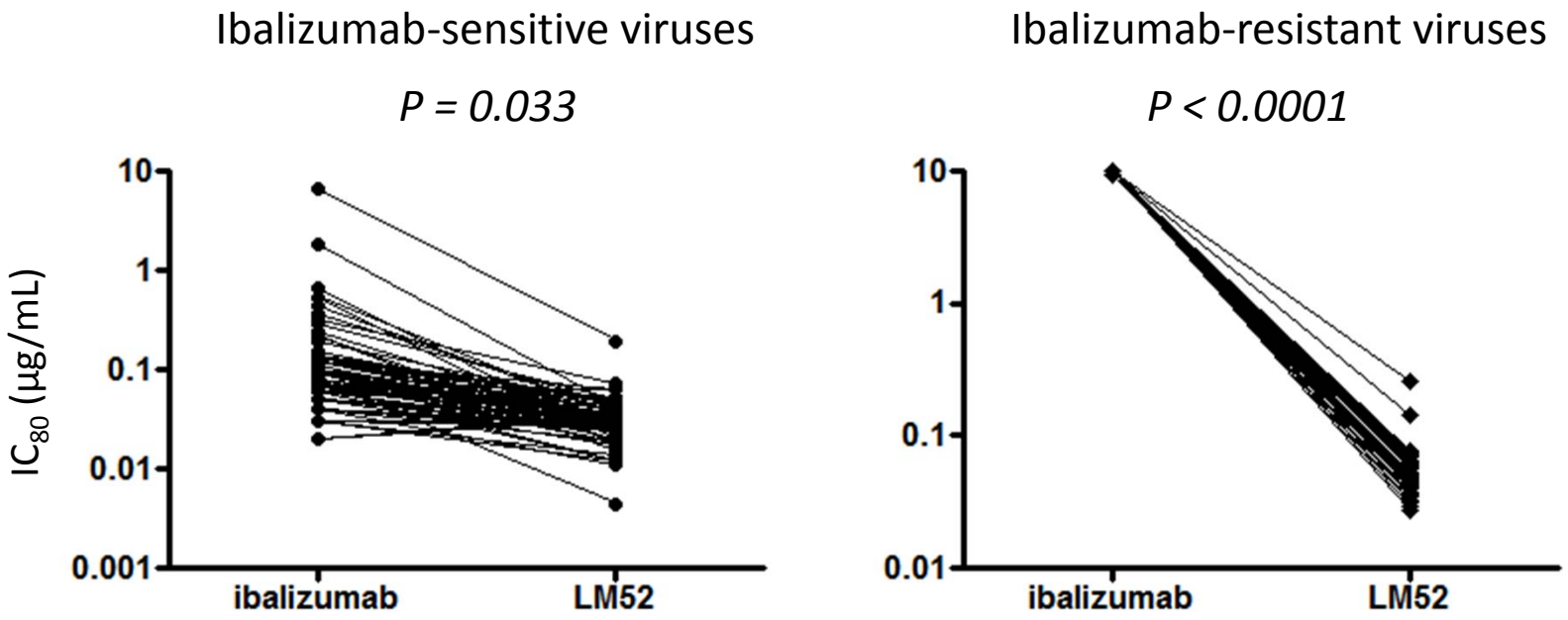
Ibalizumab-sensitive viruses
P = 0.033
Ibalizumab-resistant viruses
P < 0.0001
IC80 (µg/mL)
10
1
0.1
0.01
0.001
ibalizumab
LM52
10
1
0.1
0.01
ibalizumab
LM52

Figure S4

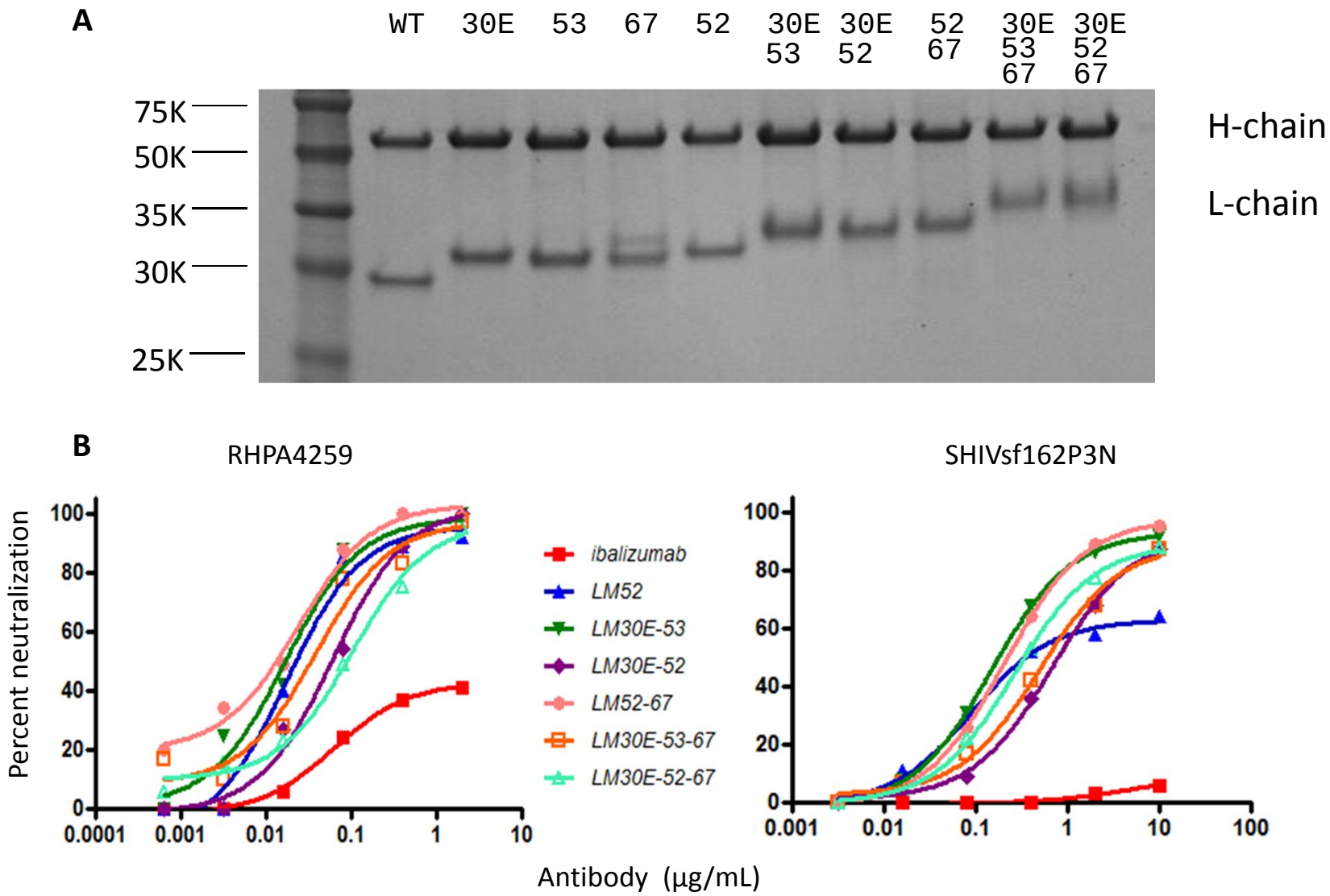
A
WT
30E
53
67
52
30E 53
30E 52
52 67
30E 53 67
30E 52 67
75K
50K
35K
30K
25K
H-chain
L-chain
B
RHPA4259
SHIVsf162P3N
Percent neutralization
ibalizumab
LM52
LM30E-53
LM30E-52
LM52-67
LM30E-53-67
LM30E-52-67
Antibody (µg/mL)

Figure S5

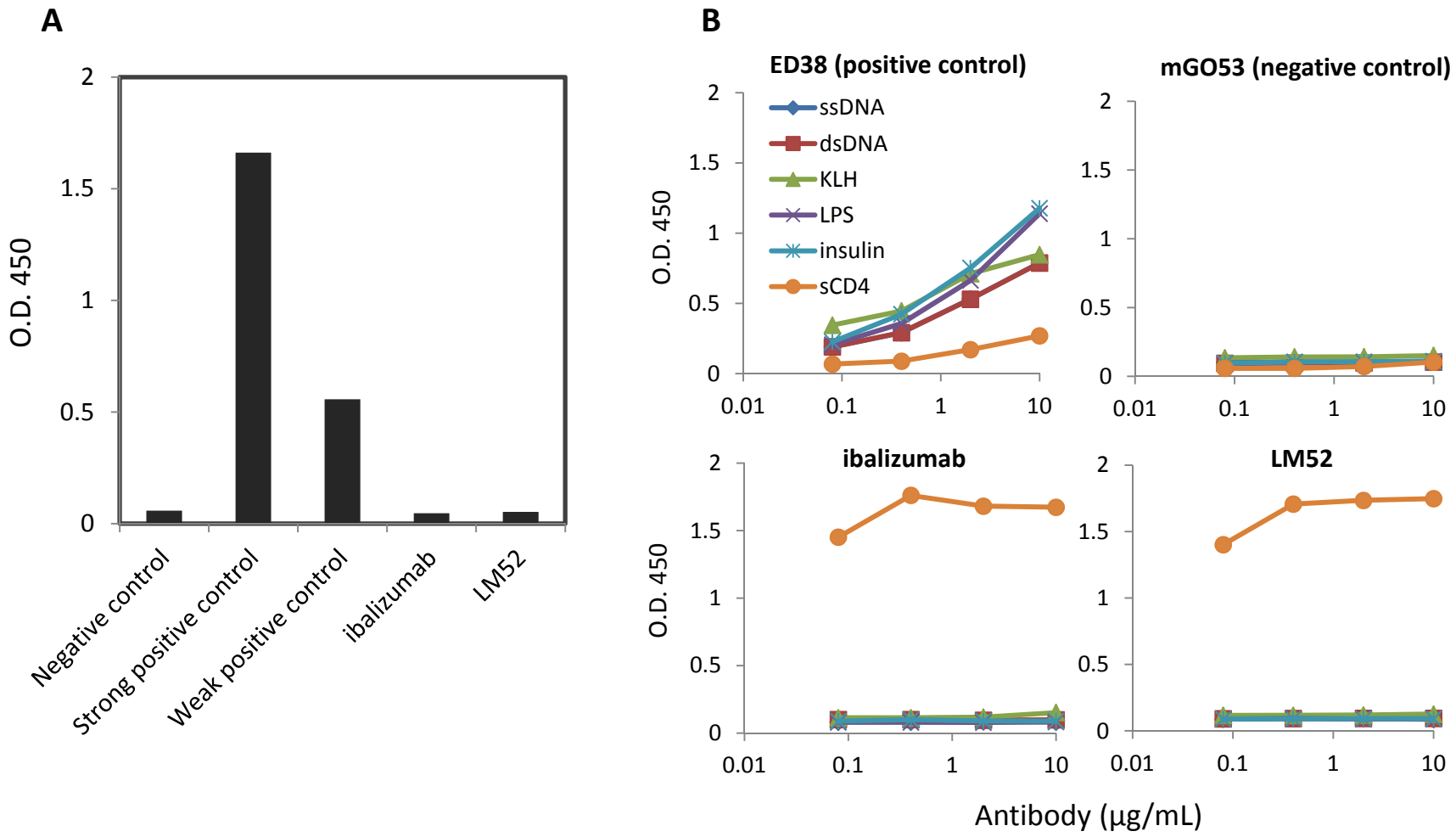
A
O.D. 450
2
1.5
1
0.5
0
Negative control
Strong positive control
Weak positive control
ibalizumab
LM52
B
ED38 (positive control)
mGO53 (negative control)
ssDNA
dsDNA
KLH
LPS
insulin
sCD4
ibalizumab
LM52
O.D. 450
0.01
0.1
1
10
Antibody (µg/mL)

Table S1. The binding kinetics of ibalizumab and its LMs to human CD4

Antibody	K_{on} (10^5/Ms)	K_{off} (10^{-5}/s)	K_D (0.1 nM)
ibalizumab	2.8	12	4.3
LM30E	1.1	15	14
LM52	4.6	16	3.5
LM53	2.9	13	4.5
LM54	3.7	27	7.3
LM60	4.4	8.3	1.9
LM65	3.3	49	15
LM67	2.5	20	8
LM76	5.0	14	2.8

Table S2. Comparison of ibalizumab and its light chain mutants

	WT	LM30E	LM52	LM53	LM54	LM65	LM67	LM60	LM76
Mean MPI (%)	75	**98**	**98**	**99**	**93**	**93**	**91**	75	78
Distance (Å) to V5		**11.1**	**19.8**	**19.8**	**23.3**	**21.3**	**18.9**	27.6	31.2
IC_{80} (μg/mL) Geometric mean	0.87	**0.14**	**0.05**	**0.09**	**0.28**	**0.20**	**0.05**	1.5	0.75

Table S4. Comparison of the IC_{80}(μg/mL) of ibalizumab and its single, double, and triple LMs

Virus	ibalizumab	LM52	LM30E-53	LM30E-52	LM52-67	LM30E-53-67	LM30E-52-67
RHPA4259	>10	0.03	0.02	0.10	0.02	0.06	0.23
SHIVsf162P3	>10	0.37	0.32	0.61	0.37	0.68	0.89
SHIVsf162P3N	>10	>10	0.93	4.40	0.98	4.40	2.50
9015-07 A1	0.24	0.04	0.04	0.06	0.04	0.08	0.13
1051-D927 TD12	>10	0.04	0.05	0.09	0.04	0.20	0.32
Q769.d22	>10	0.13	0.15	0.29	0.11	0.47	0.49
16055-2.3	>10	0.04	0.06	0.08	0.05	0.13	0.24
246F C1G C	>10	0.07	0.10	0.22	0.02	0.30	0.49
QG393.60M	>10	0.05	0.05	0.07	0.04	0.10	0.11
ZM249M.PL1	0.22	0.05	0.06	0.12	0.05	0.10	0.13
Q259.d2.17	0.37	0.09	0.10	0.15	0.07	0.13	0.26
Q461.e2	0.61	0.09	0.10	0.14	0.09	0.16	0.18
Geometric Mean	3.20	0.10	0.09	0.18	0.07	0.22	0.31