784 **Supplemental Table 1**. List of qualifying medications that are immunosuppressive,
785 immunomodulatory, or myelosuppressive (see attached)
786

787 **Supplemental Table 2**. Clinical, demographic, viral, and specimen data for enrolled patients
788 (see attached)
789

790 **Supplemental Table 3**. Output of Cox proportional hazards model for time to last positive SARS-
791 CoV-2 rRT-PCR test
792

	Hazard Ratio	Lower 95% CI	Upper 95% CI
B cell dysfunction vs. Autoimmune/Autoinflammatory	0.315	0.154	0.644
Post-SOT/HSCT vs. Autoimmune/Autoinflammatory	0.597	0.38	0.939
AIDS vs. Autoimmune/Autoinflammatory	0.282	0.08	0.996
Malignancy vs. Autoimmune/Autoinflammatory	0.582	0.312	1.085
Age	0.994	0.981	1.008
Sex - Male vs. Female	1.035	0.7	1.529
Black vs. White	0.852	0.55	1.32
Hispanic vs. White	2.049	1.002	4.191
Other / Unknown vs. White	0.671	0.269	1.672
One or More Dose of Vaccine vs. Not Vaccinated	1.653	0.775	3.527
Baseline Antiviral Use - Yes vs. No	0.878	0.572	1.35

793
794 * Variables included in the final model were immunocompromised group, age, sex, race,

795 vaccination status, and receipt of antiviral drug at baseline (see Methods).

796

797 **Supplemental Table 4**. Within-host divergence rates by gene for synonymous, nonsynonymous,
798 and stop-codon mutations
799

Gene	Mutation type	Zero count (%)	Median divergence rate	IQR	p-value*
ORF1a	Non-synonymous	51 (58%)	0	1.34E-06	3.56E-06
	Stop	85 (97%)	0	0	1
	Synonymous	37 (42%)	1.89E-06	2.24E-05	7.37E-09
ORF1b	Non-synonymous	47 (53%)	0	1.82E-06	7.55E-07
	Stop	87 (99%)	0	0	1
	Synonymous	59 (67%)	0	1.22E-06	8.11E-05
S	Non-synonymous	51 (58%)	0	8.94E-06	3.56E-06
	Stop	87 (99%)	0	0	1
	Synonymous	53 (60%)	0	4.07E-05	7.76E-06
ORF3a	Non-synonymous	82 (93%)	0	0	1
	Stop	86 (98%)	0	0	1
	Synonymous	82 (93%)	0	0	1
E	Non-synonymous	87 (99%)	0	0	1
	Stop	88 (100%)	0	0	NA
	Synonymous	86 (98%)	0	0	1
M	Non-synonymous	77 (88%)	0	0	0.11571878
	Stop	88 (100%)	0	0	NA
	Synonymous	83 (94%)	0	0	1
ORF6	Non-synonymous	85 (97%)	0	0	1
	Stop	88 (100%)	0	0	NA
	Synonymous	85 (97%)	0	0	1
ORF7a	Non-synonymous	82 (93%)	0	0	1
	Stop	88 (100%)	0	0	NA
	Synonymous	87 (99%)	0	0	1
ORF8	Non-synonymous	81 (92%)	0	0	0.67482814
	Stop	85 (97%)	0	0	1
	Synonymous	88 (100%)	0	0	NA
N	Non-synonymous	75 (85%)	0	0	0.04985083
	Stop	87 (99%)	0	0	1
	Synonymous	82 (93%)	0	0	1

800
801
802 * Wilcoxon signed rank test for difference in divergence rate (per site per day) vs. zero,

803 Bonferroni adjusted p-value

804 **Supplemental Table 5**. Consensus mutations in SARS-CoV-2 spike among 5
805 immunocompromised patients with ≥2 sequenced specimens and >56 days of RT-PCR positivity
806

Patient	Amino acid substitution	Spike domain*	Peak frequency (patient)	Date of peak frequency (patient)	Peak frequency (global)	Date of peak frequency (global)
EV084	W64R	NTD	99%	6/2022	1%	6/2022
EV022	D80G	NTD	91%	6/2022	1%	4/2021
EV022	F157L	NTD	70%	6/2022	18%	2/2023
EV009	S255P	NTD	99%	2/2023	<1%	2/2023
EV009	R346T	RBD	99%	1/2023	94%	4/2023
EV084	K356R	RBD	100%	7/2022	<1%	11/2021
EV022	L368I	RBD	65%	4/2022	90%	4/2023
EV022	S371P	RBD	100%	7/2022	<1%	1/2022
EV022	S371F	RBD	100%	7/2022	97%	11/2022
EV084	T376A	RBD	82%	5/2022	97%	7/2023
EV022	K444N	RBD	100%	6/2022	2%	11/2022
EV138	K444N	RBD	100%	9/2022	2%	11/2022
EV138	G446R	RBD	89%	8/2022	<1%	2/2023
EV009	G446D	RBD	100%	10/2022	<1%	1/2023
EV009	N450D	RBD	99%	7/2022	3%	11/2022
EV084	N450D	RBD	99%	6/2022	3%	11/2022
EV022	L452M	RBD	100%	7/2022	2%	6/2022
EV022	L455F	RBD	70%	6/2022	<1%	8/2020
EV084	I569T	SD1/SD2	99%	6/2022	<1%	7/2023
EV022	R765L	none	71%	6/2022	<1%	2/2020
EV022	T791I	FP	95%	7/2022	1%	7/2021
EV022	D936Y	HR1	99%	7/2022	2%	4/2020
EV009	D1139N	none	94%	1/2023	<1%	10/2020

807
808 * NTD = N terminal domain, RBD = receptor binding domain, FP = fusion peptide, HR = heptad
809 repeat.
810
811 † Global mutational data from GISAID, February 2020 – April 2022
812

813 **Supplemental Table 6**. Neutralization FRNT50 of patient-derived viruses with serum pools

814

Patient and Sample Day	New Spike Mutations *	Pre-Vax Pool 1[†]	Post-Vax Pool 1[†]	Pre-Vax Pool 2[†]	Post-Vax Pool 2[†]	Pre-Vax Pool 3[†]	Post-Vax Pool 3[†]
EV138 day 20 (19 days post-bebtelovimab)	–	68	166	38	278	574	992
EV138 day 63 (62 days post-bebtelovimab)	K444N, G446R	16	45	23	114	137	302
Fold Change #	–	-4.25	-3.7	-1.7	-2.4	-4.2	-3.3
EV009 day 91	R346T	103	111	190	13	47	44
Fold Change #		ND	ND	ND	ND	ND	ND
EV022 day 13	–	15	45	44	92	91	230
EV022 day 82 (14 days post-bebtelovimab)	K444N, L452M	13	33	53	114	63	253
Fold Change#	–	-1.2	-1.4	0.8	0.8	-1.4	0.9

815

816

817 Abbreviations: FRNT, Focus reduction neutralization test

818 * New mutations at >50% frequency relative to the initial sample from the same patient

819 [†] Three pools of matched pre- and post-bivalent vaccination sera from xx individuals (pool 1), xx

820 individuals (pool 2), and xx individuals (pool 3)

821 [#] Fold change measured as the absolute reduction in serum neutralization in a patient's evolved

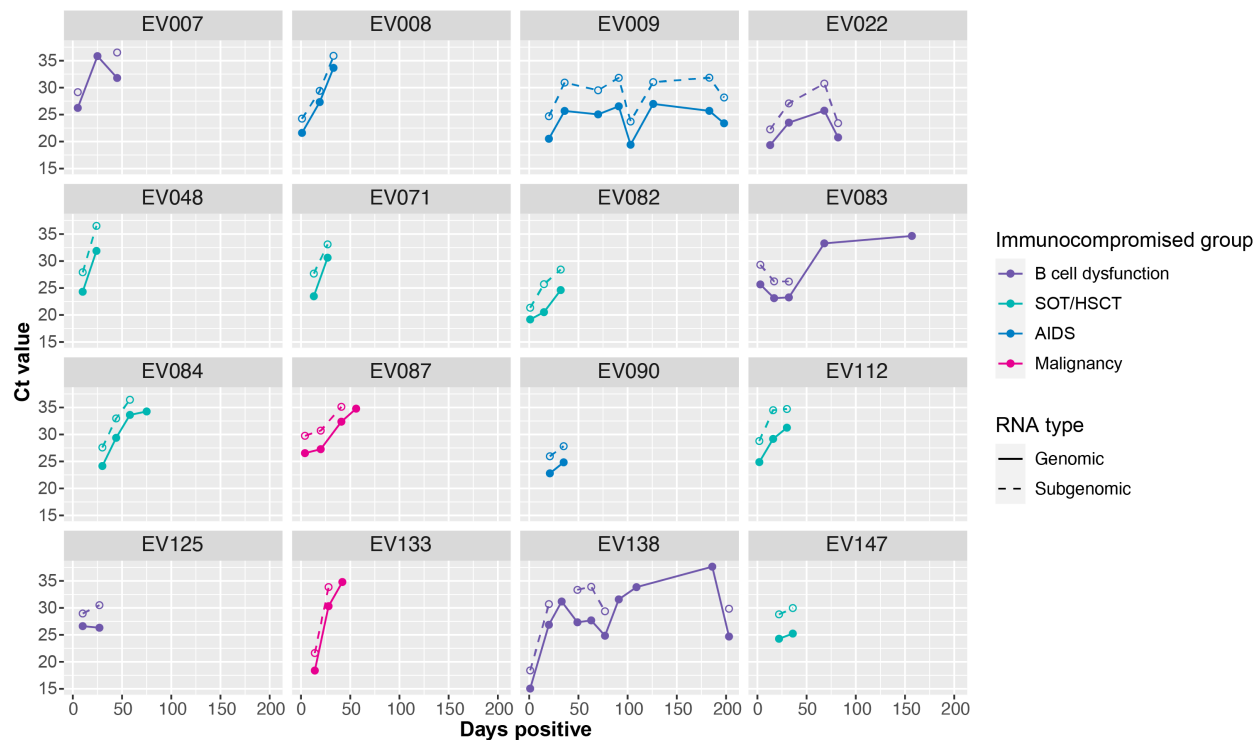822 virus relative to their initial virus

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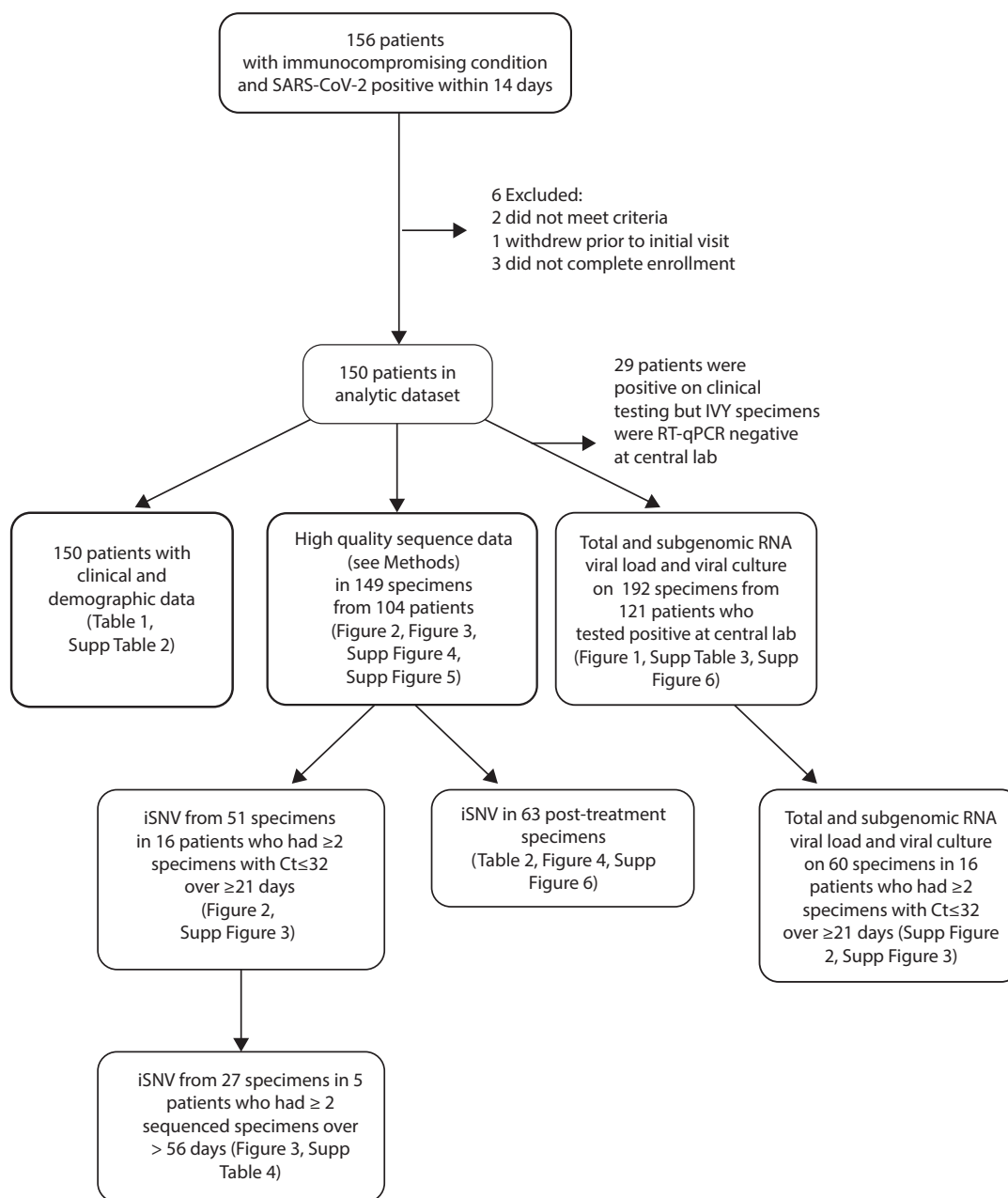
**Supplemental Figure 1**. Flow diagram of enrolled patients indicating patients and data included

in each analysis. iSNV = intrahost single nucleotide variants.

Supplemental Figure 2. Plots show total (solid line, closed circles) and subgenomic N (dotted line, open circles) RNA viral load in serial specimens (day of infection, x-axis) for each of 16 immunocompromised patients who had detectable viral RNA in ≥2 specimens spanning ≥ 21 days. Lines and points are color coded by immunocompromised group: B cell dysfunction, purple; solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT), teal; AIDS, blue; non-B cell malignancy, pink; autoimmune/autoinflammatory, orange.

840

841
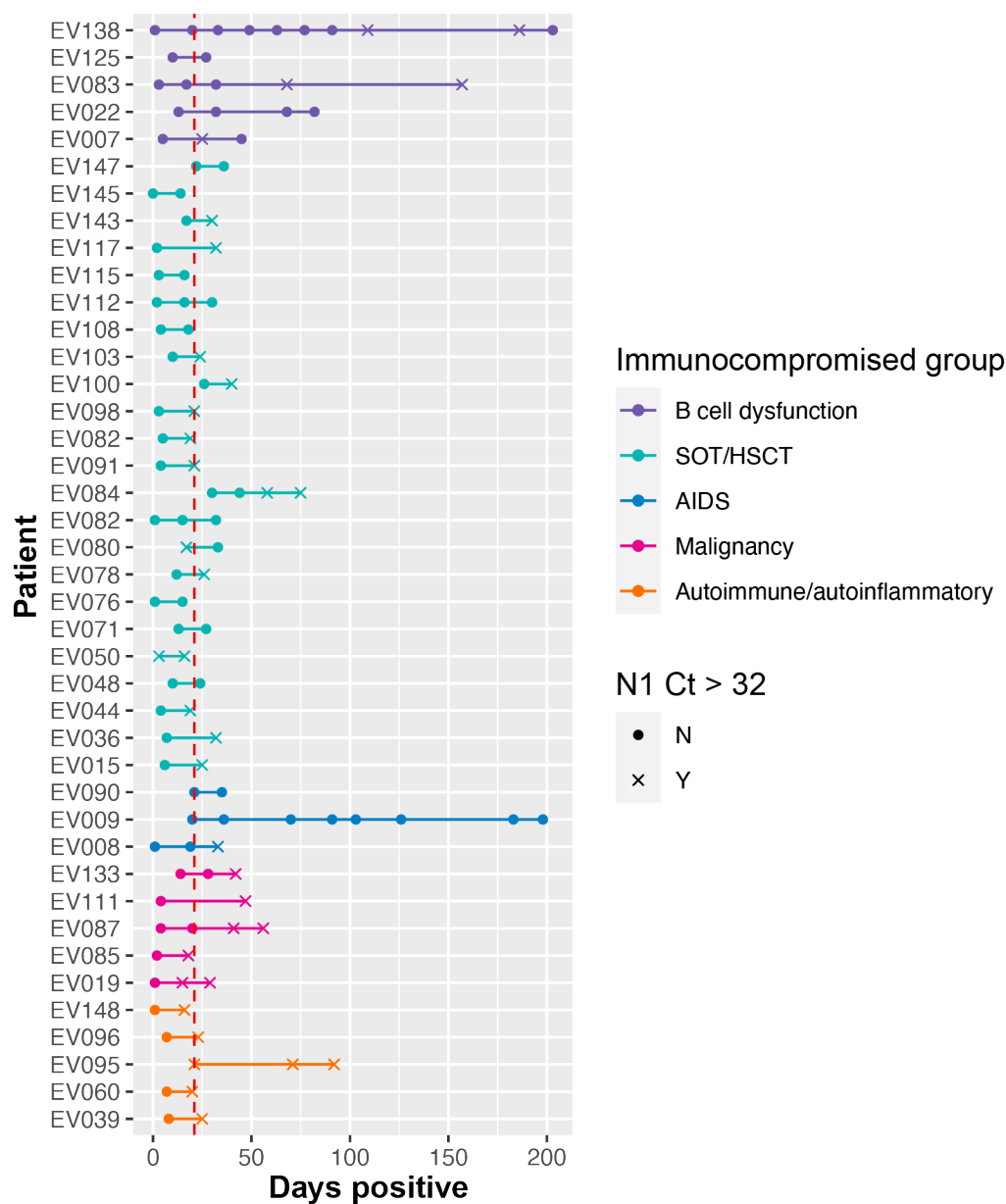
Supplemental Figure 3. Diagram identifying 16 patients with prolonged infection; defined as patients who had ≥2 sequenced specimens with rRT-PCR Ct ≤32 spanning ≥21 days. Lines and points are color-coded by immunocompromised group: B cell dysfunction, purple; solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT), teal; AIDS, blue; non-B cell malignancy, pink; autoimmune/autoinflammatory, orange. Filled circles indicate specimens with rRT-PCR Ct ≤32 and x indicate specimens with rRT-PCR Ct >32.
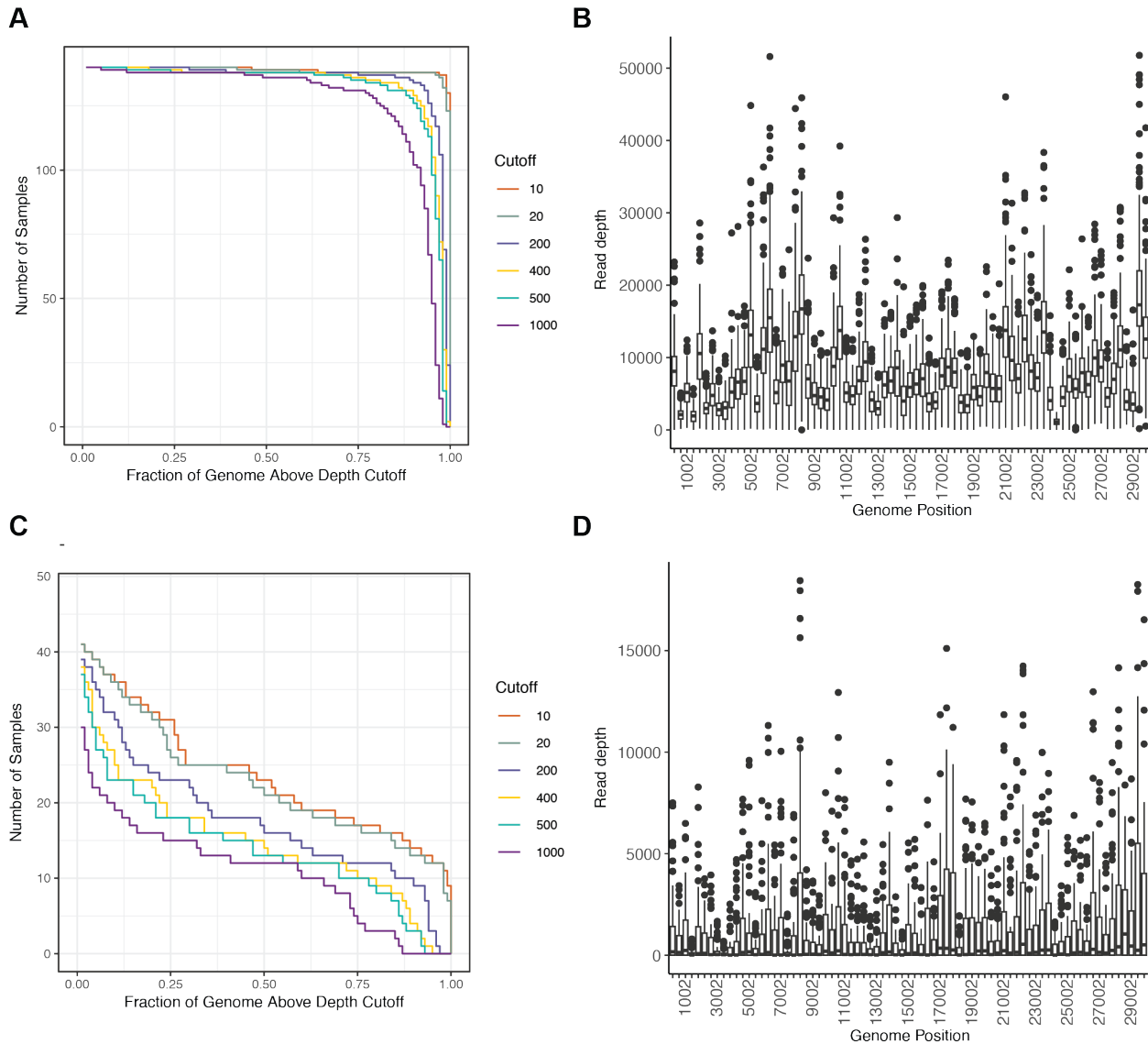
848

849

850   **Supplemental Figure 4**. Depth of coverage in sequenced specimens. Plots showing (A) number

851   of specimens (y-axis) with fraction of the genome (x-axis) covered at the indicated depths (lines,

852   legend) and (B) read depth by genomic position (sliding window) for 140 specimens with rRT-

853   PCR Ct ≤32. Plots showing (C) number of specimens (y-axis) with fraction of the genome (x-axis)

854   covered at the indicated depths (lines, legend) and (D) read depth by genomic position (sliding

855   window) for 52 specimens with rRT-PCR Ct >32.

856
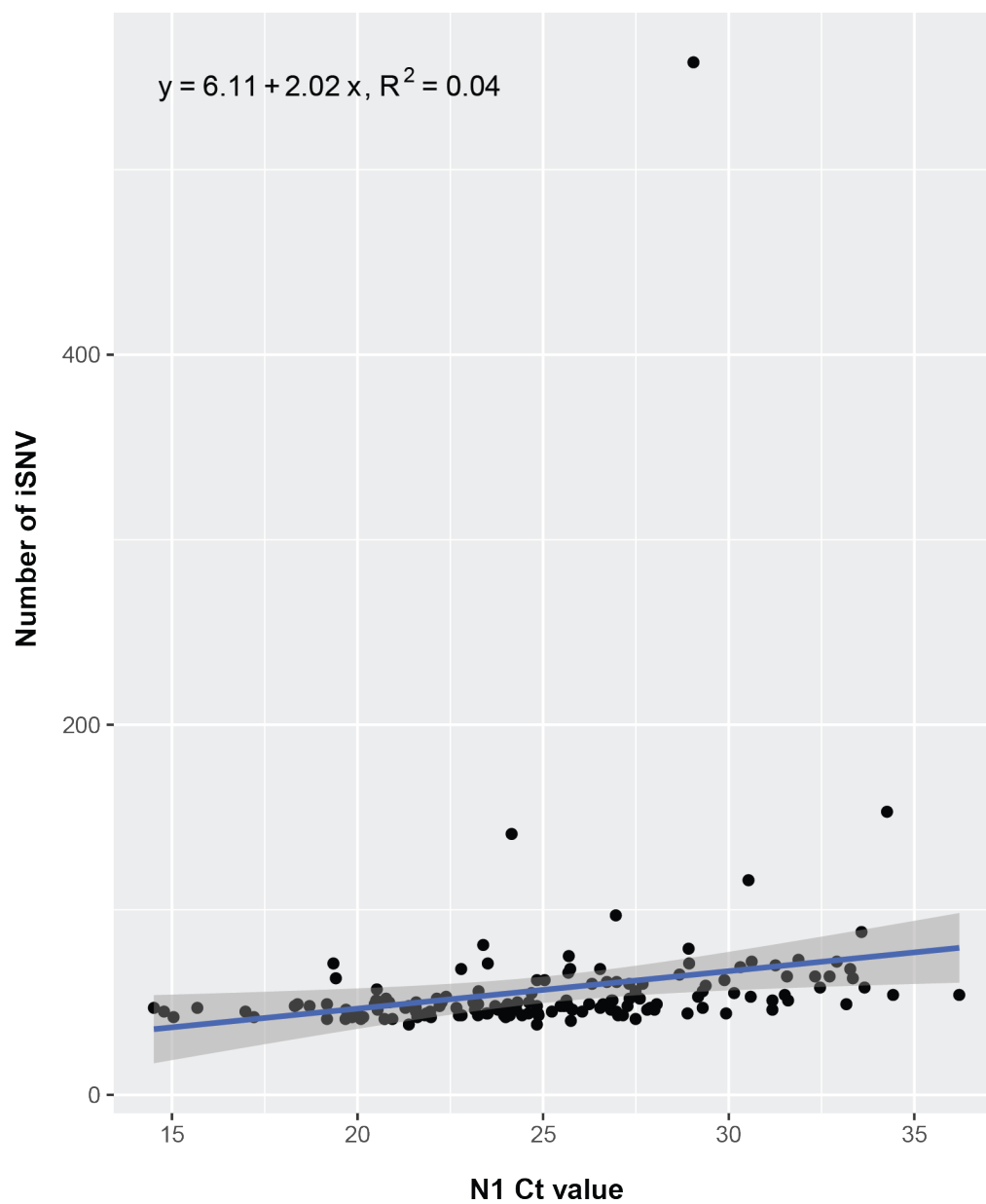
857

858

859 **Supplemental Figure 5**. Number of intrahost single nucleotide variants (iSNV) identified at 2-

860 100% frequency (y-axis) per specimen (point) as a function of total SARS-CoV-2 RNA rRT-PCR Ct

861 value. The regression line (blue), 95% confidence interval for the regression (shaded area), and

862 the equation and R^2 for the regression are indicated. The outlier point with over 500 iSNV

863 represents a single specimen from a patient previously treated with molnupiravir.

864
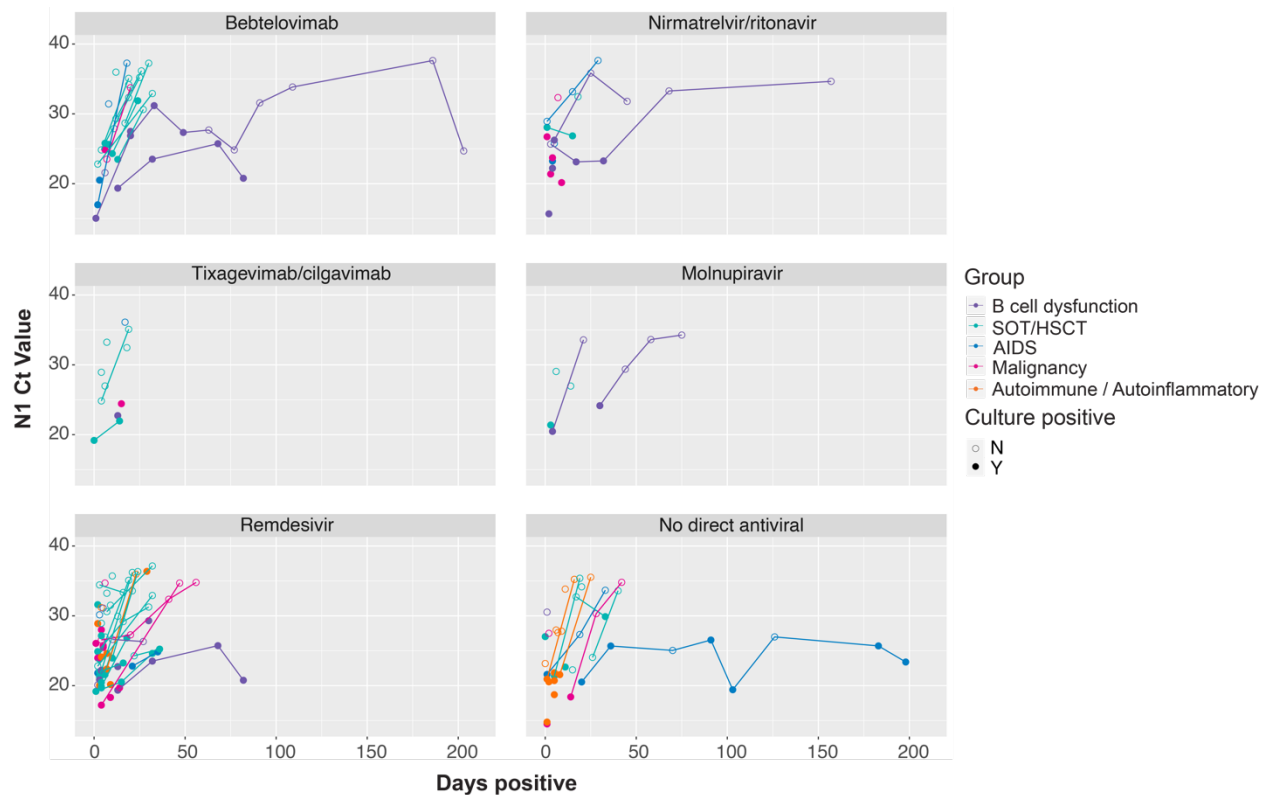
Supplemental Figure 6. Plot of SARS-CoV-2 total RNA rRT-PCR Ct values for the 115 patients receiving indicated antiviral treatments. Lines and points are color-coded by immunocompromised group: B cell dysfunction, purple; solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT), teal; AIDS, blue; non-B cell malignancy, pink; autoimmune/autoinflammatory, orange.