

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods.

Study Design and Sample Collection

For the minimum follow-up time, participants in the nirmatrelvir treated and untreated groups were required to have collected a swab at least 11 days or more after their baseline diagnostic COVID-19 test to be eligible for this analysis. The maximum follow-up time was variable among participants. When possible, we asked participants who remained PCR positive after 6 swabs (approximately 14 days since baseline diagnostic test) to continue to collect swabs until they test negative by PCR twice, which is what we defined as persistently undetectable viral load. However, not all participants were willing/able to accommodate the extra swabs (e.g., 1027), in which case we used data from all swabs that were available, even if they did not meet the criteria for persistently undetectable viral load.

For race and ethnicity, we took the self-reported demographics and grouped them into categories as follows: Black or African American, White, Other, Unknown for race and Hispanic or Latino, Not Hispanic or Latino, Other/Unknown for ethnicity. Other for race includes American Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific Islander. Race and ethnicity were assessed in this cohort as general demographic information, as well as the possibility for future analysis with this cohort that might stratify viral kinetics and mutation emergence by race and ethnicity.

eTable 1. List of Race Options Available for Participants to Self-Report in EPIC Database

| | |
|---|--------------------------|
| American Indian/Alaska Native | Skykomish |
| Asian | Snohomish |
| Native Hawaiian or Other Pacific Islander | Snoqualmie |
| Black or African American | Squaxin Island |
| White | Steilacoom |
| American Indian | Stillaguamish |
| Alaska Native | Suquamish |
| Abenaki | Swinomish |
| Algonquian | Tulalip |
| Apache | Upper Skagit |
| Arapaho | Iowa Sac and Fox |
| Arikara | Missouri Sac and Fox |
| Assiniboine | Oklahoma Sac and Fox |
| Assiniboine Sioux | Big Cypress |
| Bannock | Brighton |
| Blackfeet | Florida Seminole |
| Brotherton | Hollywood Seminole |
| Burt Lake Band | Oklahoma Seminole |
| Caddo | San Manual |
| Cahuilla | Absentee Shawnee |
| California Tribes | Eastern Shawnee |
| Canadian and Latin American Indian | Battle Mountain |
| Catawba | Duckwater |
| Cayuse | Elko |
| Chehalis | Ely |
| Chemakuan | Goshute |
| Chemehuevi | Panamint |
| Cherokee | Ruby Valley |
| Cherokee Shawnee | Skull Valley |
| Cheyenne | South Fork Shoshone |
| Cheyenne-Arapaho | Te-Moak Western Shoshone |
| Chickahominy | Timbi-Sha Shoshone |
| Chickasaw | Washakie |
| Chinook | Wind River Shoshone |
| Chippewa | Yomba |

| | |
|-----------------------------|----------------------|
| Chippewa Cree | Duck Valley |
| Chitimacha | Fallon |
| Choctaw | Fort McDermitt |
| Chumash | Blackfoot Sioux |
| Clear Lake | Brule Sioux |
| Coeur D'Alene | Cheyenne River Sioux |
| Coharie | Crow Creek Sioux |
| Colorado River | Dakota Sioux |
| Colville | Flandreau Santee |
| Comanche | Fort Peck |
| Coos, Lower Umpqua, Siuslaw | Lake Traverse Sioux |
| Coos | Lower Brule Sioux |
| Coquilles | Lower Sioux |
| Costanoan | Mdewakanton Sioux |
| Coushatta | Miniconjou |
| Cowlitz | Oglala Sioux |
| Cree | Pine Ridge Sioux |
| Creek | Pipestone Sioux |
| Croatan | Prairie Island Sioux |
| Crow | Prior Lake Sioux |
| Cupeno | Rosebud Sioux |
| Delaware | Sans Arc Sioux |
| Diegueno | Santee Sioux |
| Eastern Tribes | Sisseton-Wahpeton |
| Esselen | Sisseton Sioux |
| Fort Belknap | Spirit Lake Sioux |
| Fort Berthold | Standing Rock Sioux |
| Fort Mcdowell | Teton Sioux |
| Fort Hall | Two Kettle Sioux |
| Gabrieleno | Upper Sioux |
| Grand Ronde | Wahpekute Sioux |
| Gros Ventres | Wahpeton Sioux |
| Haliwa | Wazhaza Sioux |
| Hidatsa | Yankton Sioux |
| Hoopa | Yanktonai Sioux |
| Hoopa Extension | Ak-Chin |
| Houma | Gila Bend |
| Inaja-Cosmit | San Xavier |

| | |
|------------------|--------------------|
| Iowa | Sells |
| Iroquois | Cow Creek Umpqua |
| Juaneno | Allen Canyon |
| Kalispel | Uintah Ute |
| Karuk | Ute Mountain Ute |
| Kaw | Gay Head Wampanoag |
| Kickapoo | Mashpee Wampanoag |
| Kiowa | Alpine |
| Klallam | Carson |
| Klamath | Dresslerville |
| Konkow | Ho-chunk |
| Kootenai | Nebraska Winnebago |
| Lassik | Table Bluff |
| Long Island | Barrio Libre |
| Luiseno | Pascua Yaqui |
| Lumbee | Chukchansi |
| Lummi | Tachi |
| Maidu | Tule River |
| Makah | Cocopah |
| Maliseet | Havasupai |
| Mandan | Hualapai |
| Mattaponi | Maricopa |
| Menominee | Mohave |
| Miami | Quechan |
| Miccosukee | Yavapai |
| Micmac | Coast Yurok |
| Mission Indians | Alaska Indian |
| Miwok | Eskimo |
| Modoc | Aleut |
| Mohegan | Alaskan Athabaskan |
| Mono | Southeast Alaska |
| Nanticoke | Ahtna |
| Narragansett | Alatna |
| Navajo | Alexander |
| Nez Perce | Allakaket |
| Nomalaki | Alanvik |
| Northwest Tribes | Anvik |
| Omaha | Arctic |

| | |
|---------------------|--------------------|
| Oregon Athabaskan | Beaver |
| Osage | Birch Creek |
| Otoe-Missouria | Cantwell |
| Ottawa | Chalkyitsik |
| Paiute | Chickaloon |
| Pamunkey | Chistochina |
| Passamaquoddy | Chitina |
| Pawnee | Circle |
| Penobscot | Cook Inlet |
| Peoria | Copper Center |
| Pequot | Copper River |
| Pima | Dot Lake |
| Piscataway | Doyon |
| Pit River | Eagle |
| Pomo | Eklutna |
| Ponca | Evansville |
| Potawatomi | Fort Yukon |
| Powhatan | Gakona |
| Pueblo | Galena |
| Puget Sound Salish | Grayling |
| Quapaw | Gulkana |
| Quinault | Healy Lake |
| Rappahannock | Holy Cross |
| Reno-Sparks | Hughes |
| Round Valley | Huslia |
| Sac and Fox | Iliamna |
| Salinan | Kaltag |
| Salish | Kluti Kaah |
| Salish and Kootenai | Knik |
| Schaghticoke | Koyukuk |
| Scott Valley | Lake Minchumina |
| Seminole | Lime |
| Serrano | Mcgrath |
| Shasta | Manley Hot Springs |
| Shawnee | Mentasta Lake |
| Shinnecock | Minto |
| Shoalwater Bay | Nenana |
| Shoshone | Nikolai |

| | |
|------------------|---|
| Shoshone Paiute | Ninilchik |
| Siletz | Nondalton |
| Sioux | Northway |
| Siuslaw | Nulato |
| Spokane | Pedro Bay |
| Stewart | Rampart |
| Stockbridge | Ruby |
| Susanville | Salamatof |
| Tohono O'Odham | Seldovia |
| Tolowa | Slana |
| Tonkawa | Shageluk |
| Tygh | Stevens |
| Umatilla | Stony River |
| Umpqua | Takotna |
| Ute | Tanacross |
| Wailaki | Tanaina |
| Walla-Walla | Tanana |
| Wampanoag | Tanana Chiefs |
| Warm Springs | Tazlina |
| Wascopum | Telida |
| Washoe | Tetlin |
| Wichita | Tok |
| Wind River | Tyonek |
| Winnebago | Venetie |
| Winnemucca | Wiseman |
| Wintun | Tlingit-Haida |
| Wiyot | Tsimshian |
| Yakama | Angoon |
| Yakama Cowlitz | Central Council of Tlingit and Haida Tribes |
| Yaqui | Chilkat |
| Yavapai Apache | Chilkoot |
| Yokuts | Craig |
| Yuchi | Douglas |
| Yuman | Haida |
| Yurok | Hoonah |
| Chiricahua | Hydaburg |
| Fort Sill Apache | Kake |
| Jicarilla Apache | Kasaan |

| | |
|-----------------------------|--------------------------|
| Lipan Apache | Kenaitze |
| Mescalero Apache | Ketchikan |
| Oklahoma Apache | Klawock |
| Payson Apache | Pelican |
| San Carlos Apache | Petersburg |
| White Mountain Apache | Saxman |
| Northern Arapaho | Sitka |
| Southern Arapaho | Tenakee Springs |
| Wind River Arapaho | Tlingit |
| Fort Peck Assiniboine Sioux | Wrangell |
| Oklahoma Cado | Yakutat |
| Agua Caliente Cahuilla | Metlakatla |
| Augustine | Greenland Eskimo |
| Cabazon | Inupiat Eskimo |
| Los Coyotes | Siberian Eskimo |
| Morongo | Yupik Eskimo |
| Santa Rosa Cahuilla | Ambler |
| Torres-Martinez | Anaktuvuk |
| Cahto | Anaktuvuk Pass |
| Chimariko | Arctic Slope Inupiat |
| Coast Miwok | Arctic Slope Corporation |
| Digger | Atkasuk |
| Kawaiisu | Barrow |
| Kern River | Bering Straits Inupiat |
| Mattole | Brevig Mission |
| Red Wood | Buckland |
| Santa Rosa | Chinik |
| Takelma | Council |
| Wappo | Deering |
| Yana | Elim |
| Yuki | Golovin |
| Canadian Indian | Inalik Diomede |
| Central American Indian | Inupiaq |
| French American Indian | Kaktovik |
| Mexican American Indian | Kawerak |
| South American Indian | Kiana |
| Spanish American Indian | Kivalina |
| Hoh | Kobuk |

| | |
|---|------------------------|
| Quileute | Kotzebue |
| Cherokee Alabama | Koyuk |
| Cherokees of Northeast Alabama | Kwiguk |
| Cherokees of Southeast Alabama | Mauneluk Inupiat |
| Eastern Cherokee | Nana Inupiat |
| Echota Cherokee | Noatak |
| Etowah Cherokee | Nome |
| Northern Cherokee | Noorvik |
| Tuscola | Nuiqsut |
| United Keetowah Band of Cherokee | Point Hope |
| Western Cherokee | Point Lay |
| Northern Cheyenne | Selawik |
| Southern Cheyenne | Shaktoolik |
| Eastern Chickahominy | Shishmaref |
| Western Chickahominy | Shungnak |
| Clatsop | Solomon |
| Columbia River Chinook | Teller |
| Kathlamet | Unalakleet |
| Upper Chinook | Wainwright |
| Wakiakum Chinook | Wales |
| Willapa Chinook | White Mountain |
| Wishram | White Mountain Inupiat |
| Bad River | Mary's Igloo |
| Bay Mills Chippewa | Gambell |
| Bois Forte | Savoonga |
| Burt Lake Chippewa | Siberian Yupik |
| Fond du Lac | Akiachak |
| Grand Portage | Akiak |
| Grand Traverse Band of Ottawa/Chippewa | Alakanuk |
| Keweenaw | Aleknagik |
| Lac Courte Oreilles | Andreaafsky |
| Lac du Flambeau | Aniak |
| Lac Vieux Desert Chippewa | Atmautluak |
| Lake Superior | Bethel |
| Leech Lake | Bill Moore's Slough |
| Little Shell Chippewa | Bristol Bay Yupik |
| Mille Lacs | Calista Yupik |

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|-------------------------------|----------------------------|
| Minnesota Chippewa | Chefornak |
| Ontonagon | Chevak |
| Red Cliff Chippewa | Chuathbaluk |
| Red Lake Chippewa | Clark's Point |
| Saginaw Chippewa | Crooked Creek |
| St. Croix Chippewa | Dillingham |
| Sault Ste. Marie Chippewa | Eek |
| Sokoagon Chippewa | Ekuk |
| Turtle Mountain | Ekwok |
| White Earth | Emmonak |
| Rocky Boy's Chippewa Cree | Goodnews Bay |
| Clifton Choctaw | Hooper Bay |
| Jena Choctaw | Iqurmuit (Russian Mission) |
| Mississippi Choctaw | Kalskag |
| Mowa Band of Choctaw | Kasigluk |
| Oklahoma Choctaw | Kipnuk |
| Santa Ynez | Koliganek |
| Oklahoma Comanche | Kongiganak |
| Alabama Coushatta | Kotlik |
| Alabama Creek | Kwethluk |
| Alabama Quassarte | Kwigillingok |
| Eastern Creek | Levelock |
| Eastern Muscogee | Lower Kalskag |
| Kialegee | Manokotak |
| Lower Muscogee | Marshall |
| Machis Lower Creek Indian | Mekoryuk |
| Poarch Band | Mountain Village |
| Principal Creek Indian Nation | Naknek |
| Star Clan of Muscogee Creeks | Napaumute |
| Thlopthlocco | Napakiak |
| Tuckabachee | Napaskiak |
| Agua Caliente | Newhalen |
| Eastern Delaware | New Stuyahok |
| Lenni-Lenape | Newtok |
| Munsee | Nightmute |
| Oklahoma Delaware | Nunapitchukv |
| Rampough Mountain | Oscarville |
| Sand Hill | Pilot Station |

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|-----------------------------|---------------------------|
| Campo | Pitkas Point |
| Capitan Grande | Platinum |
| Cuyapaibe | Portage Creek |
| La Posta | Quinhagak |
| Manzanita | Red Devil |
| Mesa Grande | St. Michael |
| San Pasqual | Scammon Bay |
| Santa Ysabel | Sheldon's Point |
| Sycuan | Sleetmute |
| Attacapa | Stebbins |
| Biloxi | Togiak |
| Georgetown (Eastern Tribes) | Toksook |
| Moor | Tulukskak |
| Nansemond | Tuntutuliak |
| Natchez | Tununak |
| Nausu Waiwash | Twin Hills |
| Nipmuc | Georgetown (Yupik-Eskimo) |
| Paugussett | St. Mary's |
| Pocomoke Acohonock | Umkumiate |
| Southeastern Indians | Alutiiq Aleut |
| Susquehanock | Bristol Bay Aleut |
| Tunica Biloxi | Chugach Aleut |
| Waccamaw-Siousan | Eyak |
| Wicomico | Koniag Aleut |
| Atsina | Sugpiaq |
| Trinity | Suqpiq |
| Whilkut | Unangan Aleut |
| Iowa of Kansas-Nebraska | Tatitlek |
| Iowa of Oklahoma | Ugashik |
| Cayuga | Chignik |
| Mohawk | Chignik Lake |
| Oneida | Egegik |
| Onondaga | Igiugig |
| Seneca | Ivanof Bay |
| Seneca Nation | King Salmon |
| Seneca-Cayuga | Kokhanok |
| Tonawanda Seneca | Perryville |
| Tuscarora | Pilot Point |

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|---------------------|---------------------|
| Wyandotte | Port Heiden |
| Oklahoma Kickapoo | Chenega |
| Texas Kickapoo | Chugach Corporation |
| Oklahoma Kiowa | English Bay |
| Jamestown | Port Graham |
| Lower Elwha | Akhiok |
| Port Gamble Klallam | Agdaagux |
| Matinecock | Karluk |
| Montauk | Kodiak |
| Poospatuck | Larsen Bay |
| Setauket | Old Harbor |
| La Jolla | Ouzinkie |
| Pala | Port Lions |
| Pauma | Akutan |
| Pechanga | Aleut Corporation |
| Soboba | Aleutian |
| Twenty-Nine Palms | Aleutian Islander |
| Temecula | Atka |
| Mountain Maidu | Belkofski |
| Nishinam | Chignik Lagoon |
| Illinois Miami | King Cove |
| Indiana Miami | False Pass |
| Oklahoma Miami | Nelson Lagoon |
| Aroostook | Nikolski |
| Alamo Navajo | Pauloff Harbor |
| Canoncito Navajo | Qagan Toyagungin |
| Ramah Navajo | Qawalangin |
| Alsea | St. George |
| Celilo | St. Paul |
| Columbia | Sand Point |
| Kalapuya | South Naknek |
| Molala | Unalaska |
| Talakamish | Unga |
| Tenino | Asian Indian |
| Tillamook | Bangladeshi |
| Wenatchee | Bhutanese |
| Yahooskin | Burmese |
| Burt Lake Ottawa | Cambodian |

| | |
|------------------------------|-------------------|
| Michigan Ottawa | Chinese |
| Oklahoma Ottawa | Taiwanese |
| Bishop | Filipino |
| Bridgeport | Hmong |
| Burns Paiute | Indonesian |
| Cedarville | Japanese |
| Fort Bidwell | Korean |
| Fort Independence | Laotian |
| Kaibab | Malaysian |
| Las Vegas | Okinawan |
| Lone Pine | Pakistani |
| Lovelock | Sri Lankan |
| Malheur Paiute | Thai |
| Moapa | Vietnamese |
| Northern Paiute | Iwo Jiman |
| Owens Valley | Maldivian |
| Pyramid Lake | Nepalese |
| San Juan Southern Paiute | Singaporean |
| Southern Paiute | Madagascar |
| Summit Lake | Black |
| Utu Utu Gwaitu Paiute | African American |
| Walker River | African |
| Yerington Paiute | Bahamian |
| Indian Township | Barbadian |
| Pleasant Point Passamaquoddy | Dominican |
| Oklahoma Pawnee | Dominica Islander |
| Oklahoma Peoria | Haitian |
| Marshantucket Pequot | Jamaican |
| Gila River Pima-Maricopa | Tobagoan |
| Salt River Pima-Maricopa | Trinidadian |
| Central Pomo | West Indian |
| Dry Creek | Botswanan |
| Eastern Pomo | Ethiopian |
| Kashia | Liberian |
| Northern Pomo | Namibian |
| Scotts Valley | Nigerian |
| Stonyford | Zairean |
| Sulphur Bank | Polynesian |

| | |
|-------------------------|---------------------------------|
| Nebraska Ponca | Micronesian |
| Oklahoma Ponca | Melanesian |
| Citizen Band Potawatomi | Other Pacific Islander |
| Forest County | Native Hawaiian |
| Hannahville | Samoaan |
| Huron Potawatomi | Tahitian |
| Pokagon Potawatomi | Tongan |
| Prairie Band | Tokelauan |
| Wisconsin Potawatomi | Guamanian or Chamorro |
| Acoma | Guamanian |
| Arizona Tewa | Chamorro |
| Cochiti | Mariana Islander |
| Hopi | Marshallese |
| Isleta | Palauan |
| Jemez | Carolinian |
| Keres | Kosraean |
| Laguna | Pohnpeian |
| Nambe | Saipanese |
| Picuris | Kiribati |
| Piro | Chuukese |
| Pojoaque | Yapese |
| San Felipe | Fijian |
| San Ildefonso | Papua New Guinean |
| San Juan Pueblo | Solomon Islander |
| San Juan De | New Hebrides |
| San Juan | European |
| Sandia | Middle Eastern or North African |
| Santa Ana | Arab |
| Santa Clara | Armenian |
| Santo Domingo | English |
| Taos | French |
| Tesuque | German |
| Tewa | Irish |
| Tigua | Italian |
| Zia | Polish |
| Zuni | Scottish |
| Duwamish | Assyrian |
| Kikiallus | Egyptian |

| | |
|---------------|--------------|
| Lower Skagit | Iranian |
| Muckleshoot | Iraqi |
| Nisqually | Lebanese |
| Nooksack | Palestinian |
| Port Madison | Syrian |
| Puyallup | Afghanistani |
| Samish | Israeli |
| Sauk-Suiattle | Other Race |
| Skokomish | Unknown |

eTable 2. List of Ethnicity Options Available for Participants to Self-Report in EPIC Database

| | | |
|------------------------|-------------------------|-----------------------|
| Hispanic or Latino | Canarian | Chilean |
| Not Hispanic or Latino | Spanish Basque | Colombian |
| Spaniard | Mexican American | Ecuadorian |
| Mexican | Mexicano | Paraguayan |
| Central American | Chicano | Peruvian |
| South American | La Raza | Uruguayan |
| Latin American | Mexican American Indian | Venezuelan |
| Puerto Rican | Costa Rican | South American Indian |
| Cuban | Guatemalan | Criollo |
| Dominican | Honduran | Unknown |
| Andalusian | Nicaraguan | |
| Asturian | Panamanian | |
| Castillian | Salvadoran | |
| Catalonian | Central American Indian | |
| Belearic Islander | Canal Zone | |
| Gallego | Argentinean | |
| Valencian | Bolivian | |

eTable 3. List of *nsp5* Nirmatrelvir (NTV) Resistance Mutations of Interest Included in This Analysis These mutations were compiled from the Stanford Coronavirus Antiviral & Resistance Database. Mutations were included if they had a reduction in susceptibility to NTV of at least 2.5-fold.

| | | |
|--------|---------|-------|
| M49del | L167F | Q192G |
| G138S | P168del | Q192H |
| F140L | H172L | Q192I |
| F140S | H172N | Q192K |
| N142L | H172Q | Q192L |
| G143S | H172Y | Q192N |
| S144A | A173T | Q192P |
| S144E | A173V | Q192R |
| S144L | R188G | Q192S |
| S144P | R188S | Q192T |
| M165R | Q189I | Q192V |
| M165T | Q189K | Q192W |
| E166A | Q192A | Q192Y |
| E166G | Q192C | A194S |
| E166K | Q192D | P252L |
| E166Q | Q192E | V297A |
| E166V | Q192F | T304I |

eTable 4. List of *nsp12* Remdesivir Resistance Mutations of Interest Included in This Analysis These mutations were compiled from the Stanford Coronavirus Antiviral & Resistance Database, as well as the Food and Drug Administration’s Prescribing Information document for RDV (indicated by asterisk). Mutations were included if they had a reduction in susceptibility to RDV of at least 2.5-fold.

| |
|--------|
| E136V* |
| V166A* |
| N198S* |
| A376V |
| D484Y |
| S759A |
| V792I |
| M794I* |
| E796G |
| C799F |
| C799R |
| E802A |
| E802D |

eTable 5. Demographic Characteristics of Participants in This Subset of the POSITIVES Cohort

Abbreviations: NTV: nirmatrelvir, RDV: remdesivir

| Characteristic, No. (%) | Untreated (n=63) | NTV Treated (n=79) | RDV Treated (n=14) |
|---------------------------------------|------------------|--------------------|--------------------|
| Age, median (IQR) | 45 (33-62) | 62 (51-71) | 61 (54-70) |
| Sex | | | |
| Female | 49 (77.8) | 59 (74.7) | 6 (42.9) |
| Male | 14 (22.2) | 20 (25.3) | 8 (57.1) |
| Race | | | |
| Black/AA | 6 (9.5) | 10 (12.7) | 2 (14.3) |
| White | 43 (68.3) | 57 (72.2) | 10 (71.4) |
| Other | 14 (22.2) | 12 (15.2) | 2 (14.3) |
| Ethnicity | | | |
| Hispanic/Latino | 4 (6.3) | 6 (7.6) | 2 (14.3) |
| Non-Hispanic/Latino | 49 (77.8) | 67 (84.8) | 10 (71.4) |
| Other/Unknown | 10 (15.9) | 6 (7.6) | 2 (14.3) |
| COVID-19 Vaccines, median (IQR) | 3 (3-4) | 4 (3-5) | 2 (1-3) |
| Days since last vaccine, median (IQR) | 224 (163-325) | 155 (83-248) | 108 (54-149) |
| mAb ^a use | 0 (0) | 0 (0) | 3 (21.4) |
| Immunosuppression ^b | | | |
| Absent | 56 (88.9) | 57 (72.2) | 7 (50.0) |
| Present | 7 (11.1) | 22 (27.8) | 7 (50.0) |
| SARS-CoV-2 Variant | | | |
| BA.2 ^c | 7 (11.1) | 9 (11.4) | 4 (28.6) |
| BA.5 ^d | 19 (30.2) | 21 (26.6) | 0 (0) |
| XBB ^e | 20 (31.7) | 30 (38.0) | 2 (14.3) |
| Other | 15 (23.8) | 13 (16.4) | 8 (57.1) |
| Not yet sequenced | 2 (3.2) | 6 (7.6) | 0 (0) |
| Virologic rebound | | | |
| Absent | 60 (95.2) | 56 (70.9) | n/a |
| Present | 3 (4.8) | 23 (29.1) | n/a |

^amAb: monoclonal antibody

^b Immunosuppression was determined by clinicians who conducted a formal chart review in any participant who had an immunosuppressing condition or was taking an immunosuppressing medication

^c BA.2 includes all BA.2 subvariants

^d BA.5 includes all BA.5 subvariants

^eXBB includes all XBB subvariants

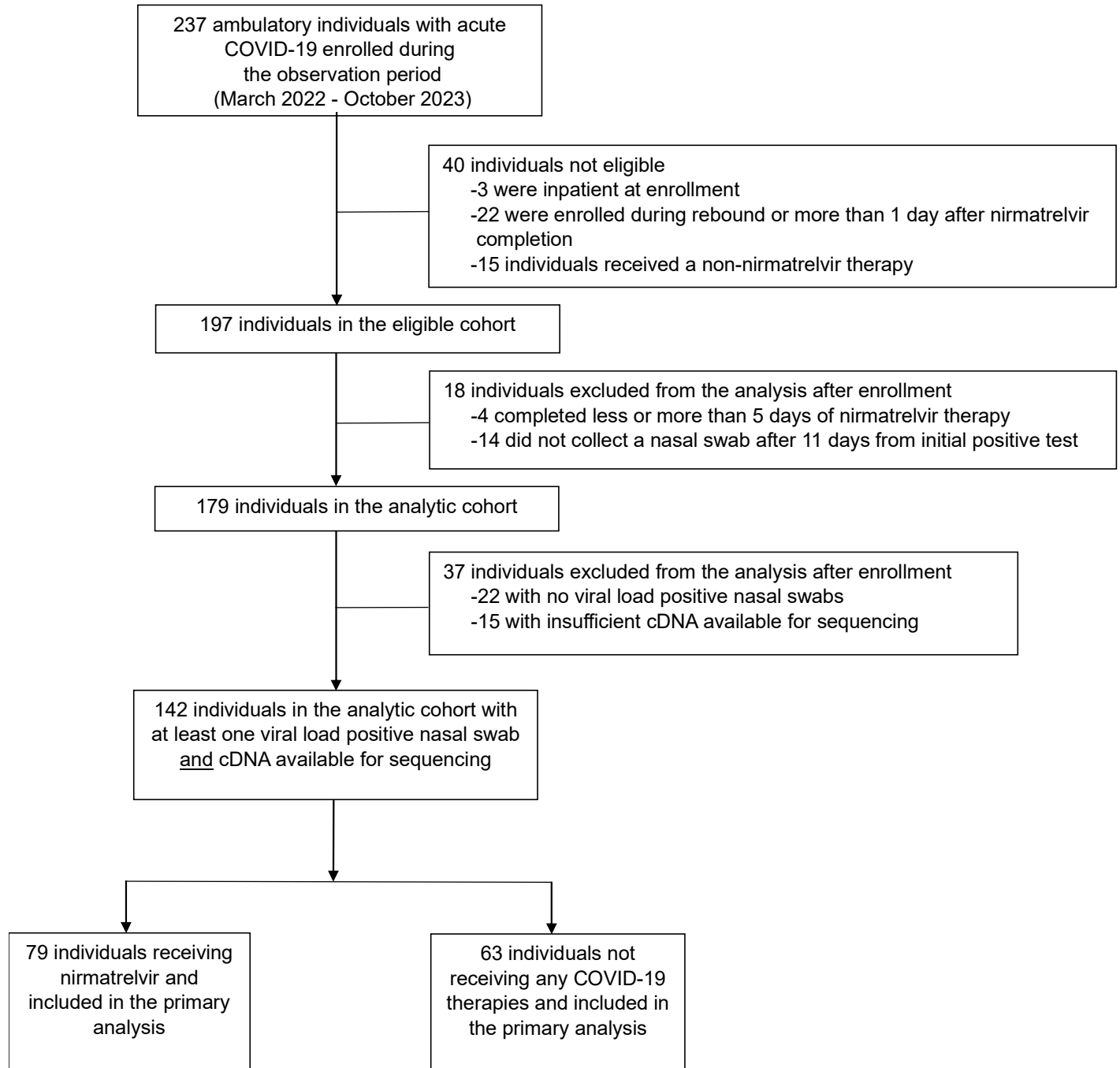
eTable 6. Immunosuppression Status and Antiviral Resistance Prevalence of Participants. Categorization of diagnoses and treatments for the immunosuppressed individuals in this study, including their antiviral treatment and their resistance mutation(s) that emerged.

| ID | SARS-CoV-2 Antiviral Treatment | Diagnosis | Immunosuppressants/Treatment | Group | Resistance Mutation(s) |
|-----|--------------------------------|---|--|-------|------------------------|
| 101 | RDV | Heart and kidney transplant | Everolimus + prednisone 5mg daily + tacrolimus | S-HT | n/a |
| 449 | RDV | Granulomatosis with polyangiitis | Rituximab | S-A | n/a |
| 459 | RDV | Immune related adverse events, metastatic merkel cell carcinoma | Pembrolizumab, tacrolimus, prednisone, mycophenolate | S-HT | M794I |
| 471 | RDV | Marginal zone lymphoma (CR) | Obinutuzumab + cyclophosphamide | S-HT | n/a |
| 475 | NTV | Multiple sclerosis | Rituximab within 12 months of COVID-19 | S-A | n/a |
| 497 | RDV | Diffuse large B-cell lymphoma (CR), hypogammaglobulinemia | Rituximab-cyclophosphamide | S-HT | n/a |
| 531 | NTV | Sarcoidosis | Infliximab | NS | n/a |
| 547 | Untreated | Rheumatoid arthritis | Tocilizumab + methotrexate | NS | n/a |
| 551 | NTV | Psoriatic arthritis | Infliximab | NS | n/a |
| 552 | NTV | Seronegative spondyloarthropathy | Adalimumab + methotrexate | NS | n/a |
| 557 | NTV | Rheumatoid arthritis, systemic lupus erythematosus | Methotrexate | NS | n/a |
| 563 | NTV | Rheumatoid arthritis | Adalimumab | NS | Q189K |
| 569 | NTV | Systemic lupus erythematosus | Hydroxychloroquine + methylprednisolone daily 6mg | NS | n/a |
| 573 | NTV | Inflammatory arthritis | Adalimumab + hydroxychloroquine | NS | n/a |
| 597 | NTV | Giant cell arteritis, polymyalgia rheumatica | Tocilizumab + prednisone orally 5mg daily | NS | Q189K |
| 658 | NTV | Rheumatoid arthritis | Tocilizumab | NS | n/a |
| 687 | NTV | Rheumatoid arthritis, systemic lupus erythematosus | Hydroxychloroquine, methotrexate | NS | n/a |
| 735 | Untreated | Psoriatic arthritis | Adalimumab | NS | n/a |
| 768 | NTV | Ankylosing spondylitis | Secukinumab | NS | Q189K |

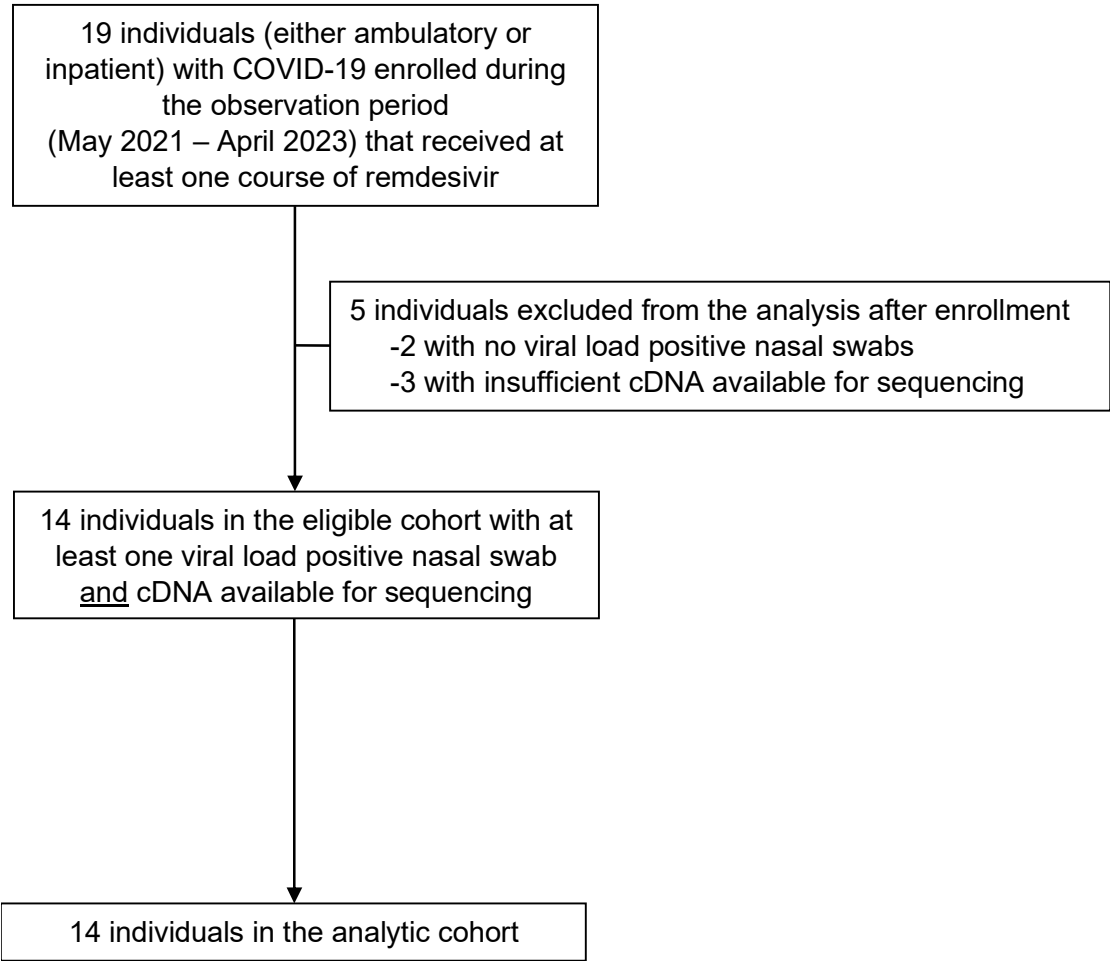
| ID | SARS-CoV-2 Antiviral Treatment | Diagnosis | Immunosuppressants/Treatment | Group | Resistance Mutation(s) |
|------|--------------------------------|---|---|-------|------------------------|
| 805 | NTV | Ulcerative colitis, inflammatory arthritis | Golimumab, methotrexate | NS | n/a |
| 870 | RDV | Mantle cell lymphoma | Bendamustine and rituximab within 12 months | S-HT | N198S, V792I, M794I |
| 945 | NTV | IgG4 related disease | Rituximab | S-A | n/a |
| 953 | Untreated | Rheumatoid arthritis | Infliximab, methotrexate, prednisone 3mg | NS | n/a |
| 1223 | RDV | Acute myeloid leukemia, hematopoietic stem cell transplantation | Tacrolimus, prednisone 10mg, venetoclax and chemotherapy until 2022 | S-HT | n/a |
| 1235 | NTV | Psoriatic arthritis | Methotrexate, etanercept | NS | n/a |
| 1236 | NTV | Systemic lupus erythematosus | Prednisone orally 5mg daily, methotrexate, hydroxychloroquine | NS | n/a |
| 1355 | NTV | Rheumatoid arthritis | Baricitinib | NS | n/a |
| 1389 | Untreated | Rheumatoid arthritis | Methotrexate, hydroxychloroquine, adalimumab | NS | n/a |
| 1399 | Untreated | Uveitis and retinal vasculitis | Methotrexate, infliximab | NS | n/a |
| 1472 | NTV | Mantle cell lymphoma | Rituximab, bendamustine | S-HT | n/a |
| 1473 | NTV | Breast cancer | Pertuzumab-trastuzumab-hyaluronidase-zzxf | NS | P252L |
| 1504 | Untreated | Breast cancer | Eribulin, fulvestrant, sacituzumab govitecan, pembrolizumab | NS | n/a |
| 1521 | NTV | Relapsing polychondritis | Azathioprine + adalimumab | NS | n/a |
| 1556 | NTV | Rheumatoid arthritis | Methotrexate, adalimumab (used etanercept in early 2023) | NS | n/a |
| 1557 | Untreated | Takayasu arteritis | Adalimumab | NS | n/a |
| 1560 | NTV | Rheumatoid arthritis | Infliximab, methotrexate | NS | V297A |

S-HT: severe hematological oncology/transplant, S-A: severe autoimmune disease/B-cell deficient, NS: non-severe immunosuppression, CR: complete remission, RDV: remdesivir, NTV: nirmatrelvir

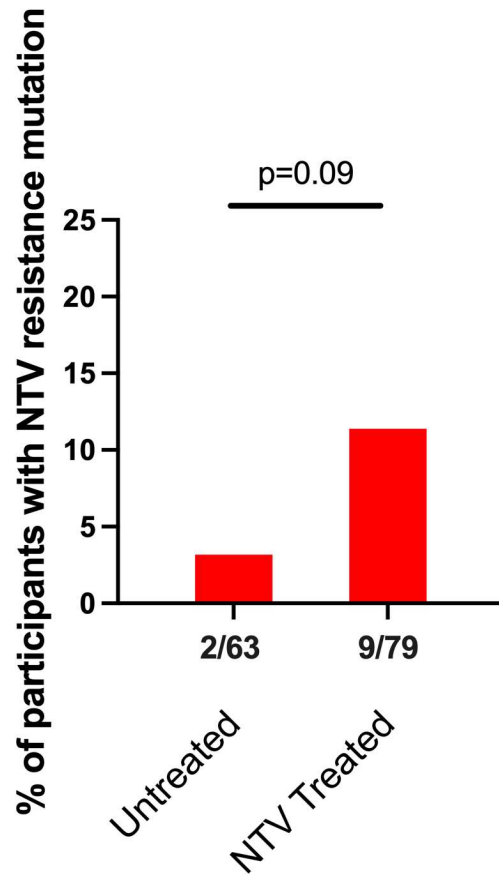
eFigure 1. Screening and Enrollment Diagram for Nirmatrelvir and Untreated Cohorts



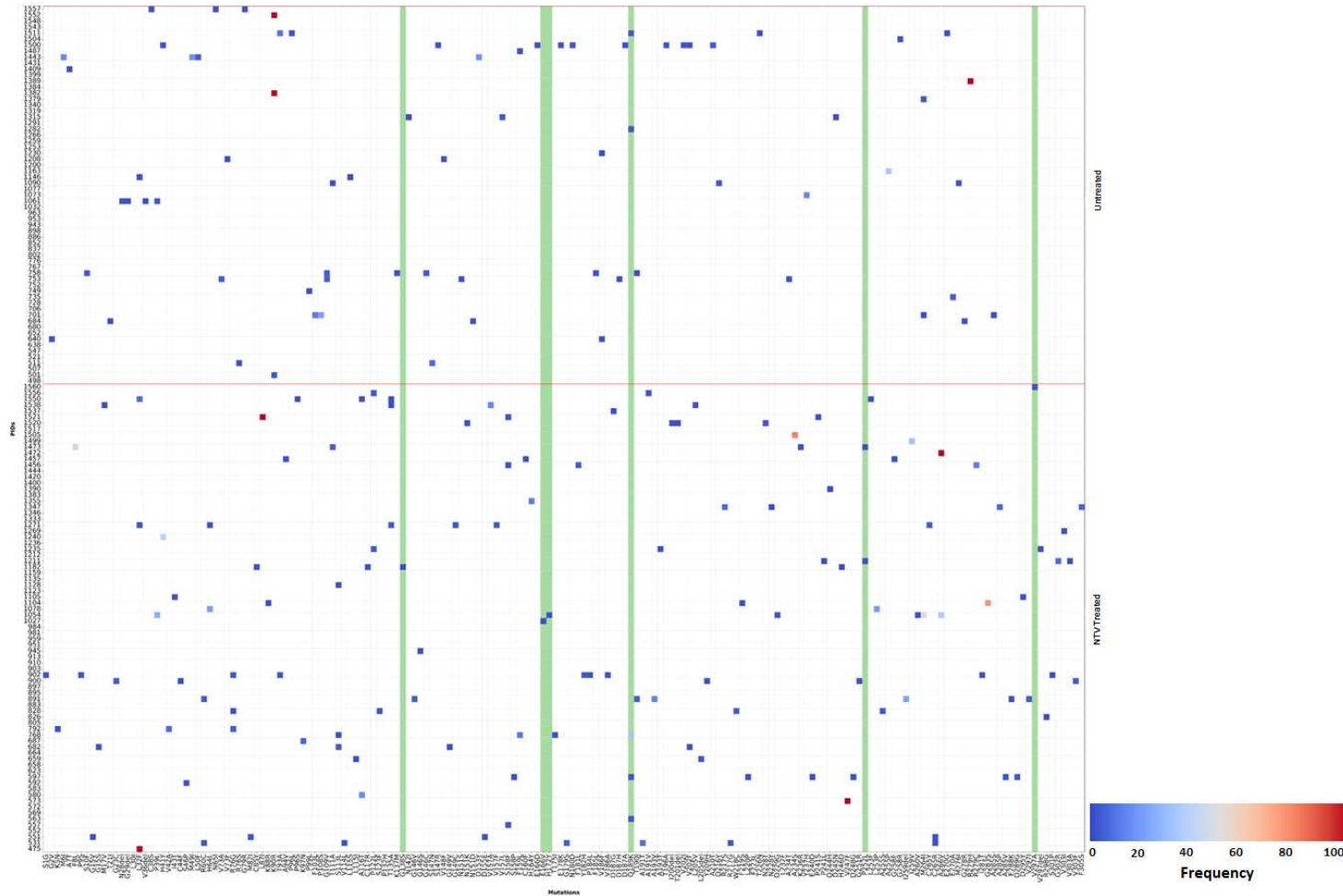
eFigure 2. Screening and Enrollment Diagram for Remdesivir Cohort



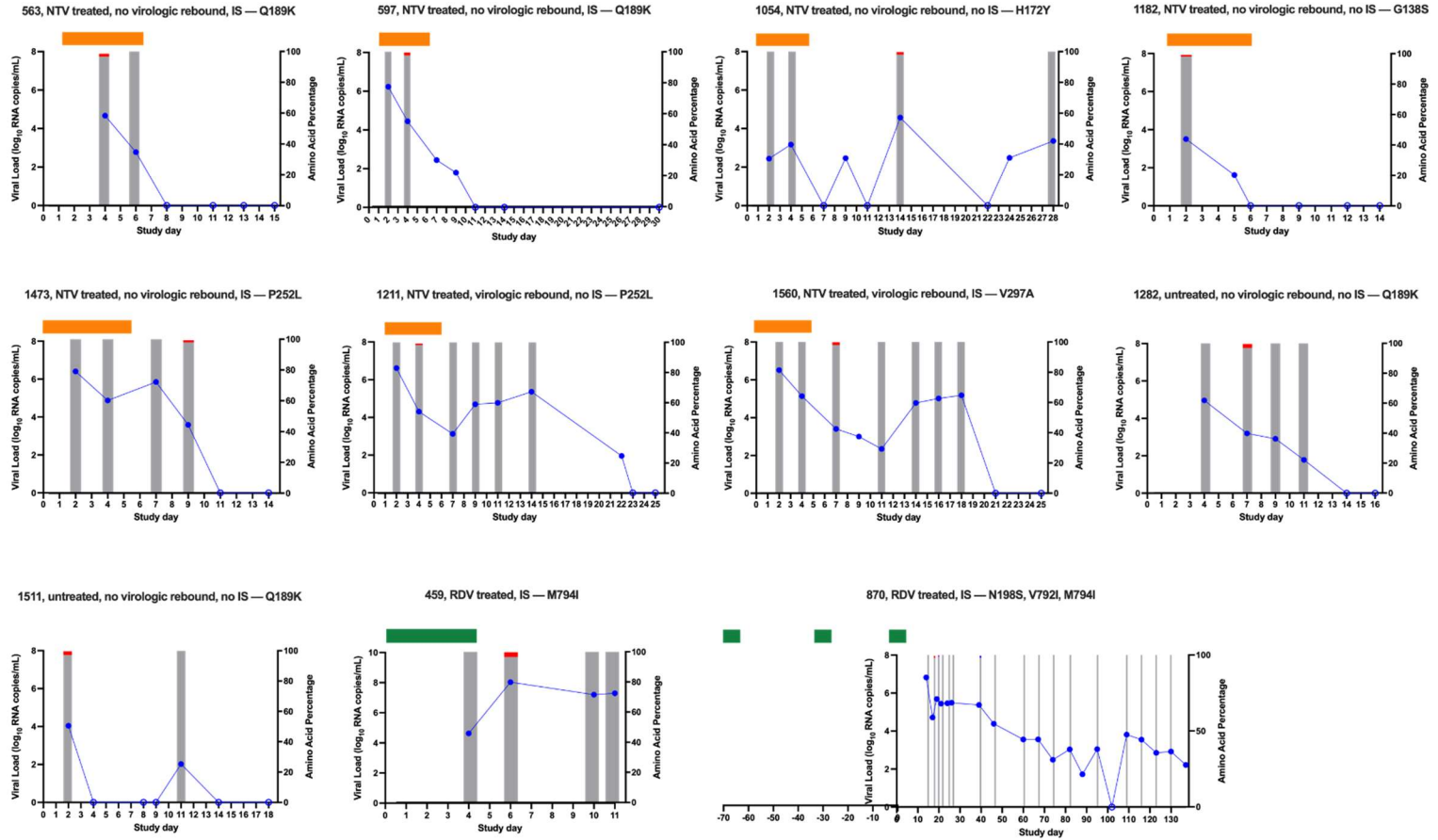
eFigure 3. Prevalence of Emergent Nirmatrelvir (NTV) Resistance Mutations in Untreated and NTV-Treated Individuals. *P* value was calculated using a two-sided Boschloo's test.



eFigure 4. Heat Map Showing Distribution of *nsp5* Polymorphisms in Untreated and Nirmatrelvir (NTV) Treated Individuals. NTV treated individuals are shown below the red line and untreated individuals are shown above the red line. Each row represents the highest frequency polymorphism that was observed across multiple timepoints of an individual. The green bars highlight the NTV resistance mutations of interest that emerged. Using our control library, a calculated threshold was set for identifying low frequency mutations at 1% for viral loads $\geq 3 \log_{10}$ SARS-CoV-2 RNA copies/mL and at 10% for viral loads $< 3 \log_{10}$ SARS-CoV-2 RNA copies/mL.



eFigure 5. Viral Load and Mutational Landscape Graphs for All the Participants With an Emergent Antiviral Resistance Mutation. Abbreviations: IS: immunosuppressed, NTV: nirmatrelvir, RDV: remdesivir.



eFigure 6. Heat Map Showing Distribution of *nsp12* Polymorphisms in Remdesivir (RDV) Treated Individuals.

Each row represents the highest frequency polymorphism that was observed across multiple timepoints of an individual. The green bars highlight the RDV resistance mutations of interest that emerged. Using our control library, a calculated threshold was set for identifying low frequency mutations at 1% for viral loads $\geq 3 \log_{10}$ SARS-CoV-2 RNA copies/mL and at 10% for viral loads $< 3 \log_{10}$ SARS-CoV-2 RNA copies/mL.

