# SARS-CoV-2 and HIV co-infection: lessons for future pandemics

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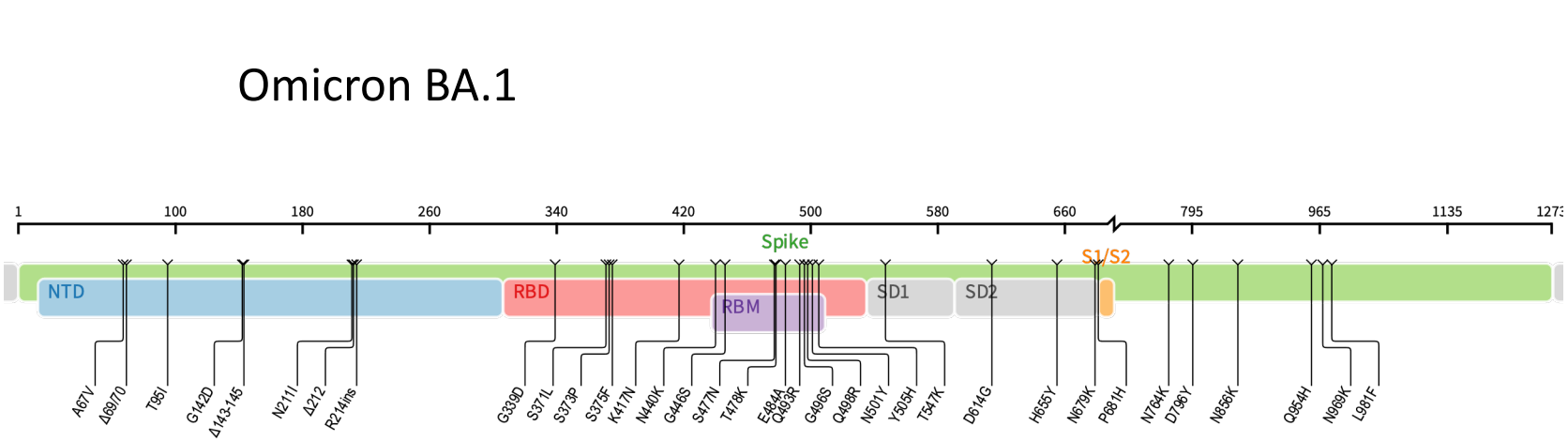
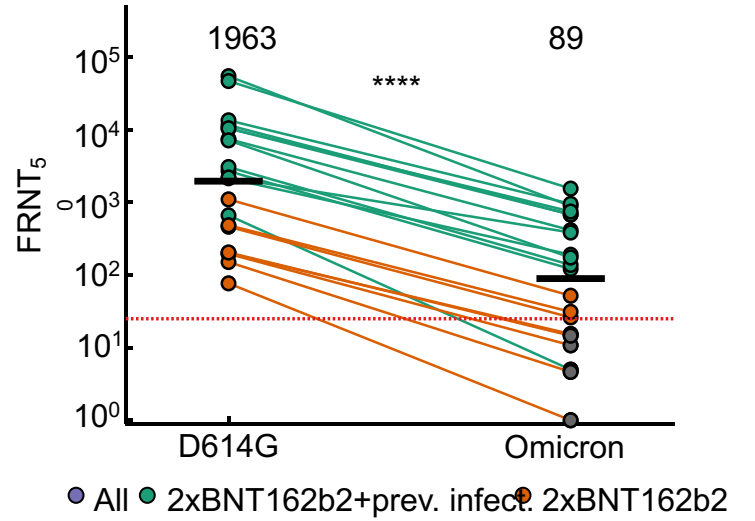
# Why is studying respiratory viruses in the context of HIV important?

- 8.5 million people living with HIV in South Africa alone
- 1 in 10 PLWH has advanced HIV disease (CD4 <200)
- ~800K immunosuppressed because of HIV
- Immunosuppression may interfere with infection clearance and lead to viral evolution of respiratory viruses

# SARS-CoV-2 variants are an example of how viral evolution plays a key role in our immune response



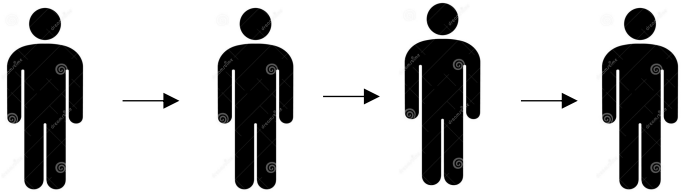




Cele…Sigal, *Nature* 2022;602:654-656

# Several possibilities for how SARS-CoV-2 evolves

Stepwise

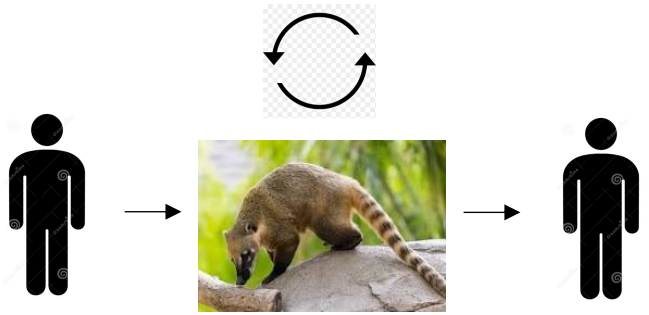
+1 mutation +1 mutation +1 mutation



Should see intermediates

Reverse zoonosis

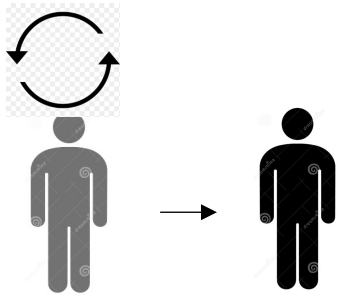
Many mutations



Coati

Immunosuppression

Many mutations



Giovanetti et al., Emerg Infect Dis. 2022 Aug;28(8):1725-1727; Zhou et al., *Cell Reports* 2022; 38, 110344; Kemp et al., Nature 2021; 592, 277-282

# Outline

- Cohort to understand the immune response to infection and vaccination
- Evolution of SARS-CoV-2 immune escape in advance HIV disease immunosuppression
- Other evolved changes in the virus

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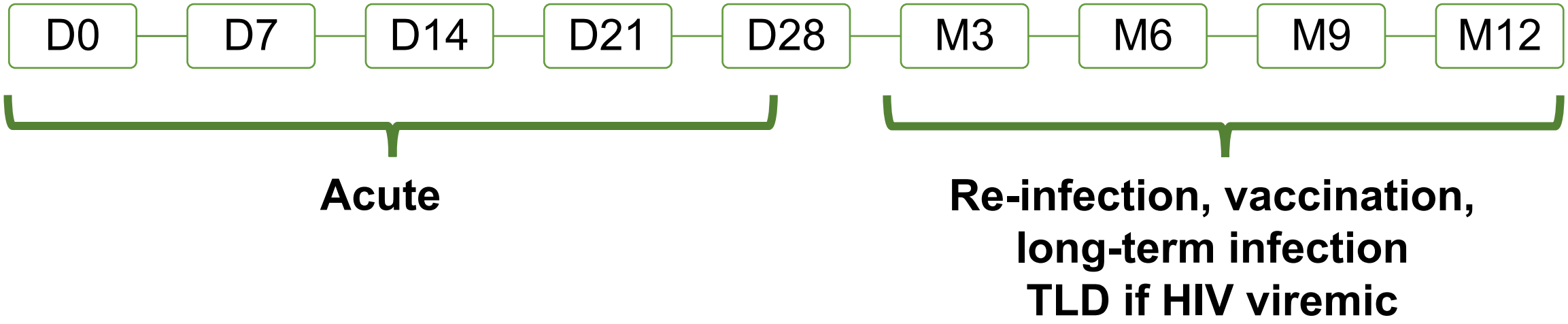
# Longitudinal cohort tracking participants from infection or vaccination

**Enrollment Sites (Durban)**

**1.Clairwood Hospital**
**2.King Edward Hospital**
**3.Inkosi Albert Luthuli Central Hospital**



# Participants vary in both HIV status and immunity

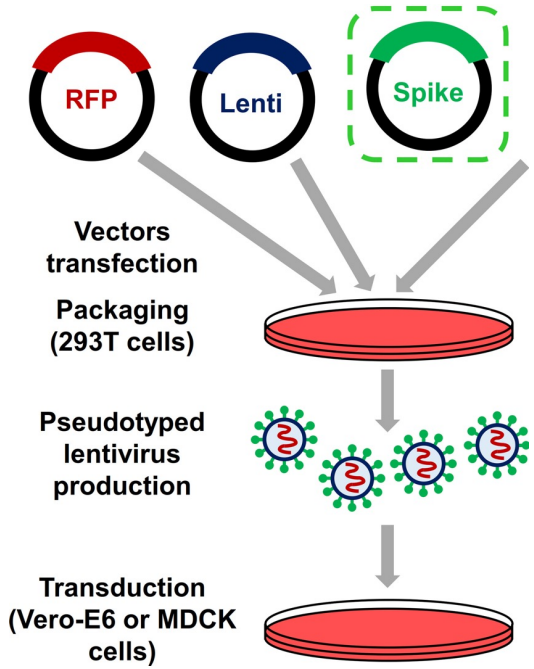
HIV status →

Immunity ↓

| | All | HIV- | HIV+ Suppressed | HIV+ Unsuppressed | Advanced HIV Disease |
|---|---|---|---|---|---|
| | **847** | **511 (60%)** | **217 (26%)** | **30 (3%)** | **89 (11%)** |
| **Age** | 42 (32-52) | 43 (32-55) | 43 (36-50.5) | 32 (27-38) | 41 (32-45) |
| **Female** | 550 (65%) | 316 (62%) | 164 (76%) | 19 (63%) | 51 (57%) |
| **SuppO2** | 134 (16%) | 59 (12%) | 34 (16%) | 7 (23%) | 34 (38%) |
| **Median CD4 count** | 786 (496-1060) | 922 (701-1149.5) | 701 (488-897.5) | 405.5 (248-540) | 58 (20.5-143) |
| **Vaccination:** | | | | | |
| **Not vaccinated** | 413 (49%) | 221 (44%) | 104 (48%) | 20 (67%) | 68 (76%) |
| **1 dose BNT162b2*** | 29 (3%) | 17 (3%) | 8 (4%) | 1 (3%) | 3 (3%) |
| **1 dose Ad26.COV2.S** | 255 (30%) | 190 (37%) | 55 (25%) | 5 (17%) | 5 (6%) |
| **2 doses BNT162b2** | 150 (18%) | 83 (16%) | 50 (23%) | 4 (13%) | 13 (15%) |
| **Variant:** | | | | | |
| **Ancestral** | 147 (17%) | 86 (17%) | 43 (20%) | 9 (30%) | 9 (10%) |
| **Beta** | 135 (16%) | 91 (18%) | 25 (12%) | 4 (13%) | 15 (17%) |
| **Delta** | 106 (13%) | 51 (10%) | 31 (14%) | 5 (17%) | 19 (21%) |
| **Omicron BA1, BA2** | 97 (11%) | 48 (9%) | 26 (12%) | 3 (10%) | 20 (23%) |
| **Omicron BA5+** | 108 (13%) | 60 (12%) | 26 (12%) | 4 (13%) | 18 (20%) |
| **None**** | 254 (30%) | 175 (34%) | 66 (30%) | 5(17%) | 8 (9%) |

# Kept it simple during the pandemic: blood and nasopharyngeal swab sampled at study visits

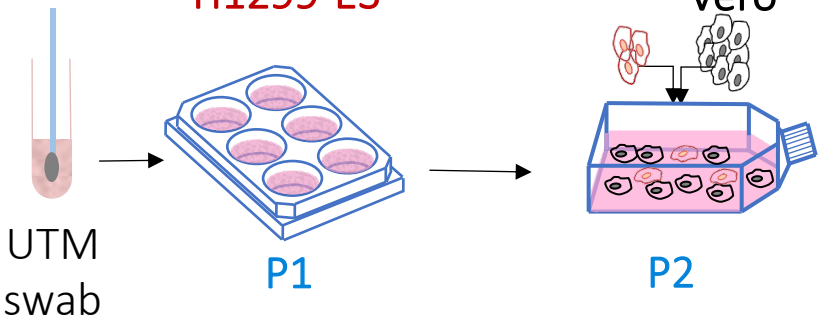
# We determined antibody response using live virus



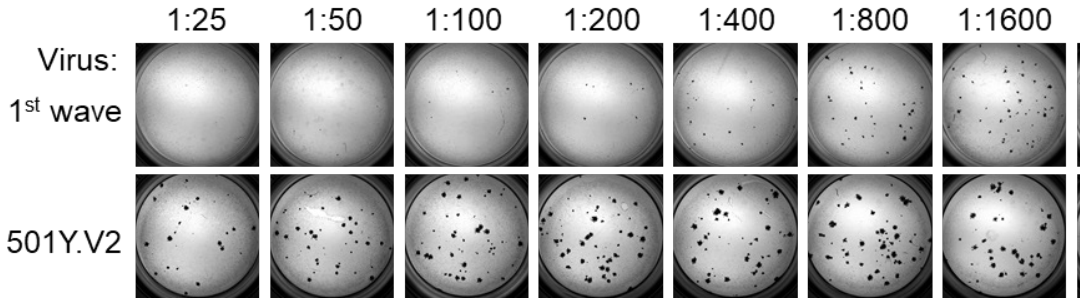

Huang et al. Biomedical Journal 2020

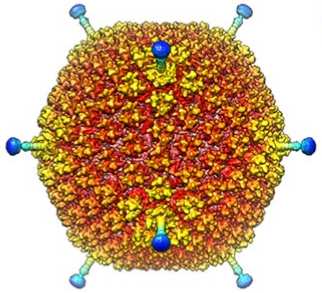
1) Covid-19 cohort n=847 including 40% PLWH

2) Pathogen isolation in BSL3 and sequencing




3) Live virus assays: antibodies/ pathogenicity



Adenovirus

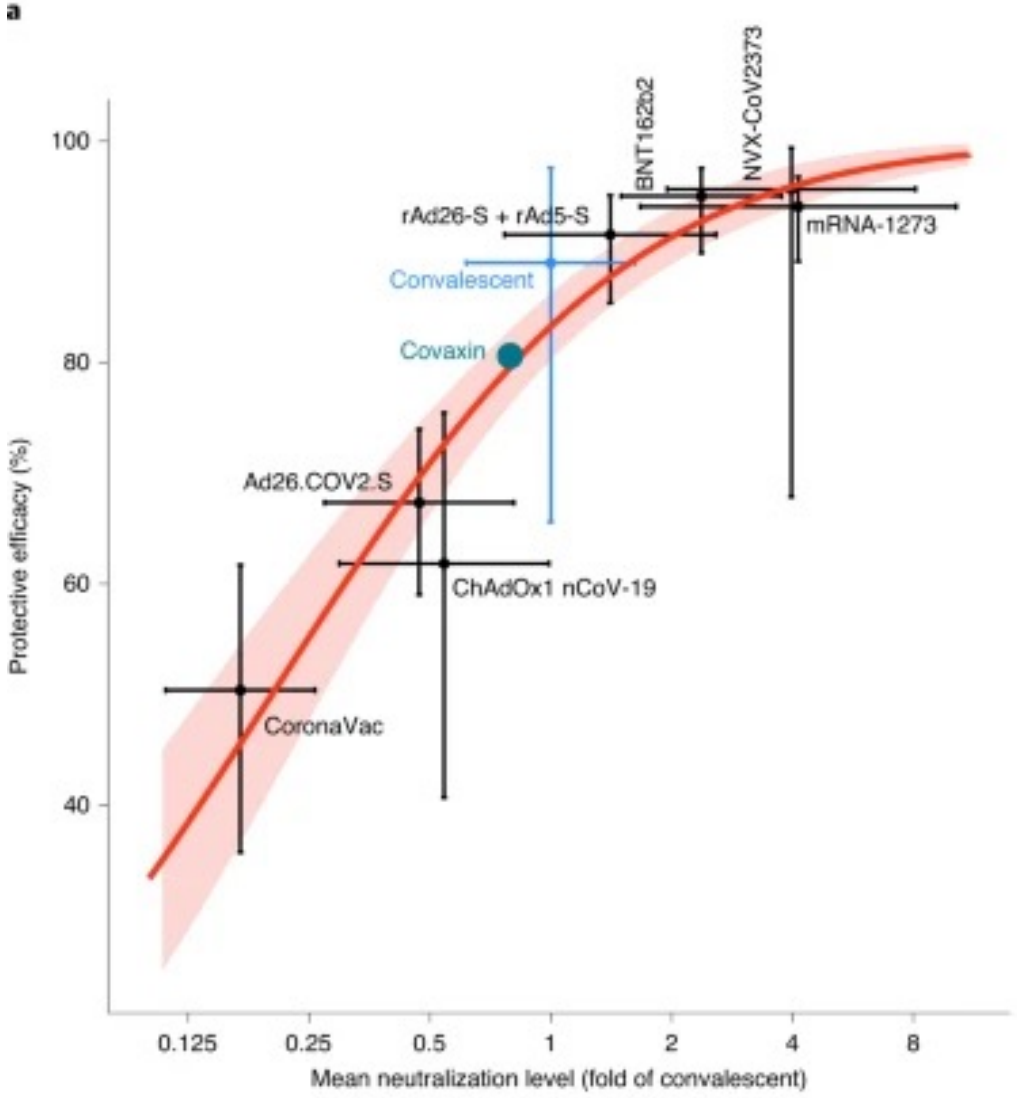
**Problems:**

**Suppressed by HIV ART**

**Pseudovirus will not work for non enveloped viruses**

Cele…Sigal, *Nature* 2021; 593(7857):142-146

# Neutralizing antibody activity is a correlate of protection for SARS-CoV-2 infection




Khoury…Davenport, Nature Med. 2021; 27: 1205–1211

# ChAdOX vaccine elicited poor neutralizing antibody activity against Beta variant…and low vaccine efficacy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2021 VOL. 384 NO. 20

## Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant

S.A. Madhi, V. Baillie, C.L. Cutland, M. Voysey, A.L. Koen, L. Fairlie, S.D. Padayachee, K. Dheda, S.L. Barnabas, Q.E. Bhorat, C. Briner, G. Kwatra, K. Ahmed, P. Aley, S. Bhikha, J.N. Bhiman, A.'.E. Bhorat, J. du Plessis, A. Esmail, M. Groenewald, E. Horne, S.-H. Hwa, A. Jose, T. Lambe, M. Laubscher, M. Malahleha, M. Masenya, M. Masilela, S. McKenzie, K. Molapo, A. Moultrie, S. Oelofse, F. Patel, S. Pillay, S. Rhead, H. Rodel, L. Rossouw, C. Taoushanis, H. Tegally, A. Thombrayil, S. van Eck, C.K. Wibmer, N.M. Durham, E.J. Kelly, T.L. Villafana, S. Gilbert, A.J. Pollard, T. de Oliveira, P.L. Moore, A. Sigal, and A. Izu, for the NGS-SA Group and the Wits–VIDA COVID Group*

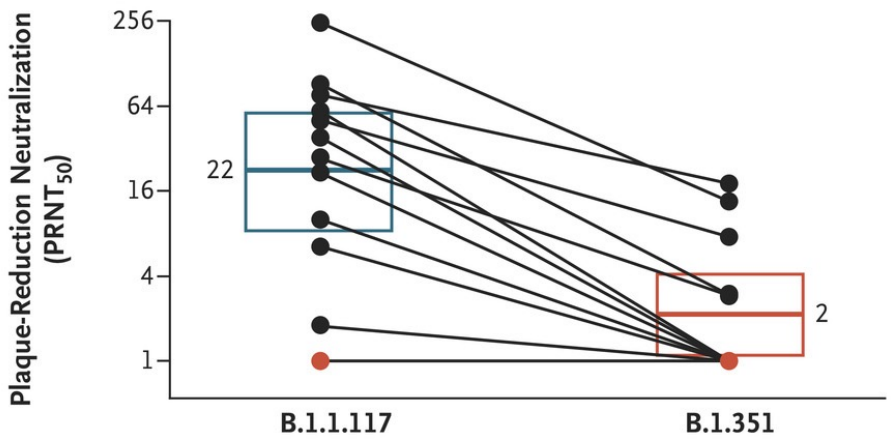
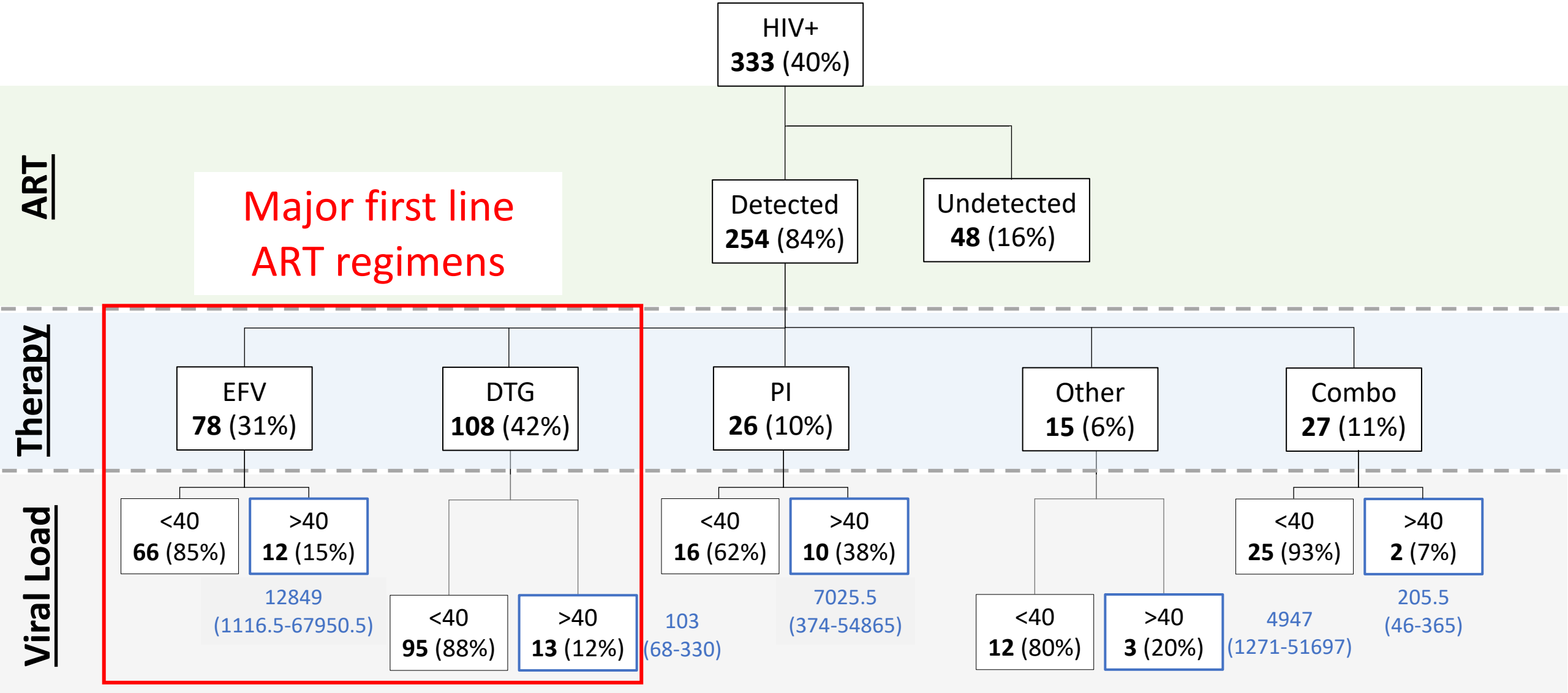



**Table 2.** Vaccine Efficacy against Mild-to-Moderate Symptomatic Covid-19 Confirmed by Nucleic Acid Amplification Test.*

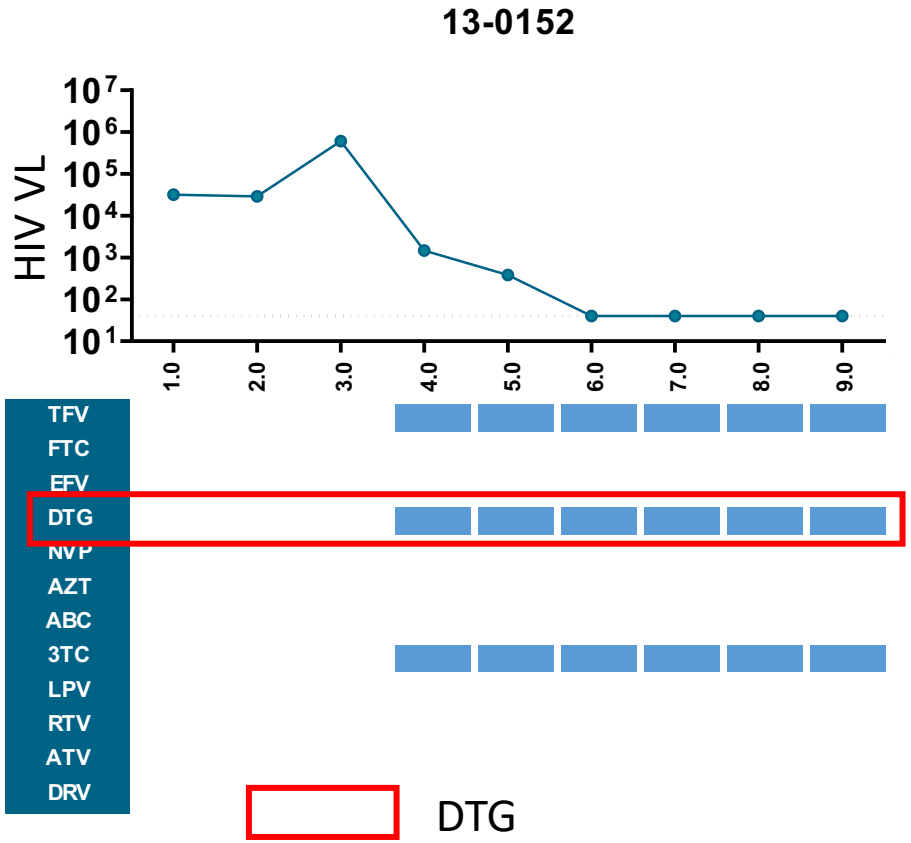
| End Point | Baseline Serologic Status† | Total No. of Cases | Placebo | Incidence Risk | Vaccine | Incidence Risk | Vaccine Efficacy‡ |
|---|---|---|---|---|---|---|---|
| | | | *no./total no. (%)* | *per 1000 person-yr (person-days)* | *no./total no. (%)* | *per 1000 person-yr (person-days)* | *% (95% CI)* |
| Mild-to-moderate illness with onset >14 days after second injection | Seronegative | 42 | 23/717 (3.2) | 93.6 (89,714) | 19/750 (2.5) | 73.1 (94,881) | 21.9 (–49.9 to 59.8) |
| Mild-to-moderate illness associated with B.1.351 variant with onset >14 days after second injection | Seronegative | 39 | 20/714 (2.8) | 81.6 (89,448) | 19/750 (2.5) | 73.1 (94,881) | 10.4 (–76.8 to 54.8) |

# Most participants in the study adhere to ART and begin or continue to suppress HIV

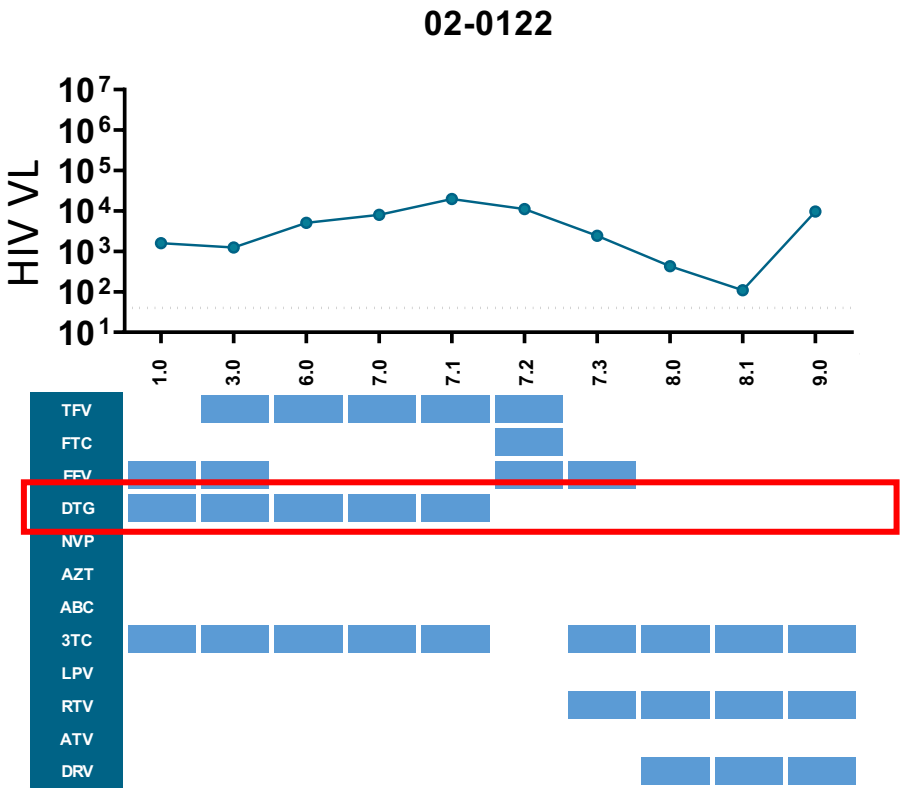


# Some participants do not suppress HIV post-ART initiation for reasons which are difficult to control – some cases of persistent HIV viremia remain

Example of suppression




Example of failure




Results from mass spectrometry

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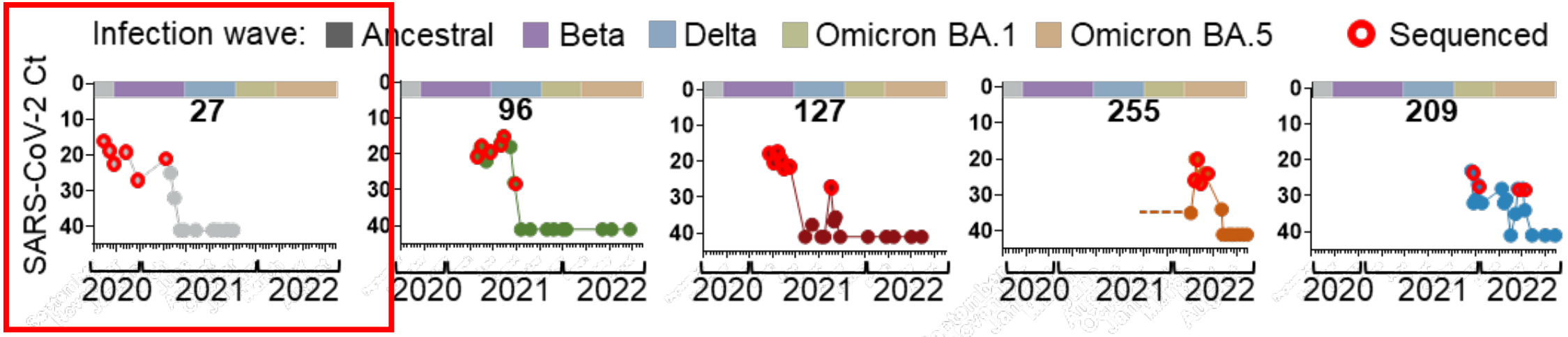
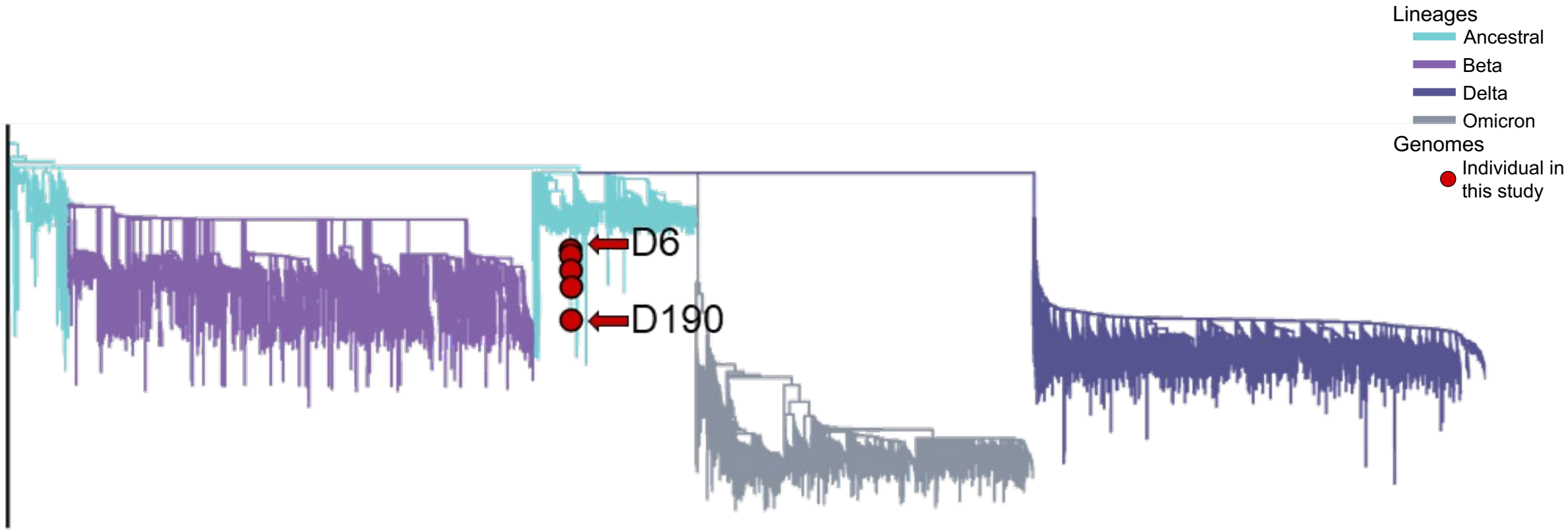
- Other evolved changes in the virus

# Advanced HIV disease participants had long-term SARS-CoV-2 infections with different variants

| Participant | Sex | Age | Diagnosis | Infection wave | Enrol. CD4 | Enrol. HIV VL |
|---|---|---|---|---|---|---|
| **27** | F | 36 | Sep 2020 | D614G | 6 | 34151 |
| **96** | M | 42 | Apr 2021 | Beta | 4 | 111883 |
| **127** | M | 34 | Mar 2021 | Beta | 12 | 8581 |
| **209** | F | 35 | Dec 2021 | Omicron | 24 | 423817 |
| **255** | M | 20 | Sep 2021 | Delta | 2 | 12041 |

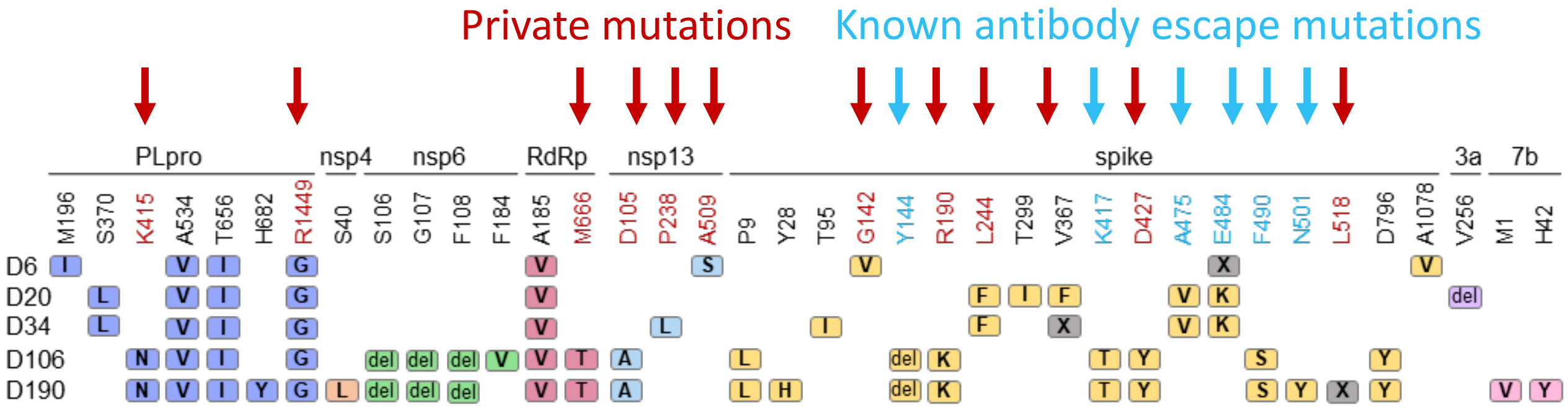


# Advanced HIV disease participant infected with ancestral virus had continuous 6-month infection

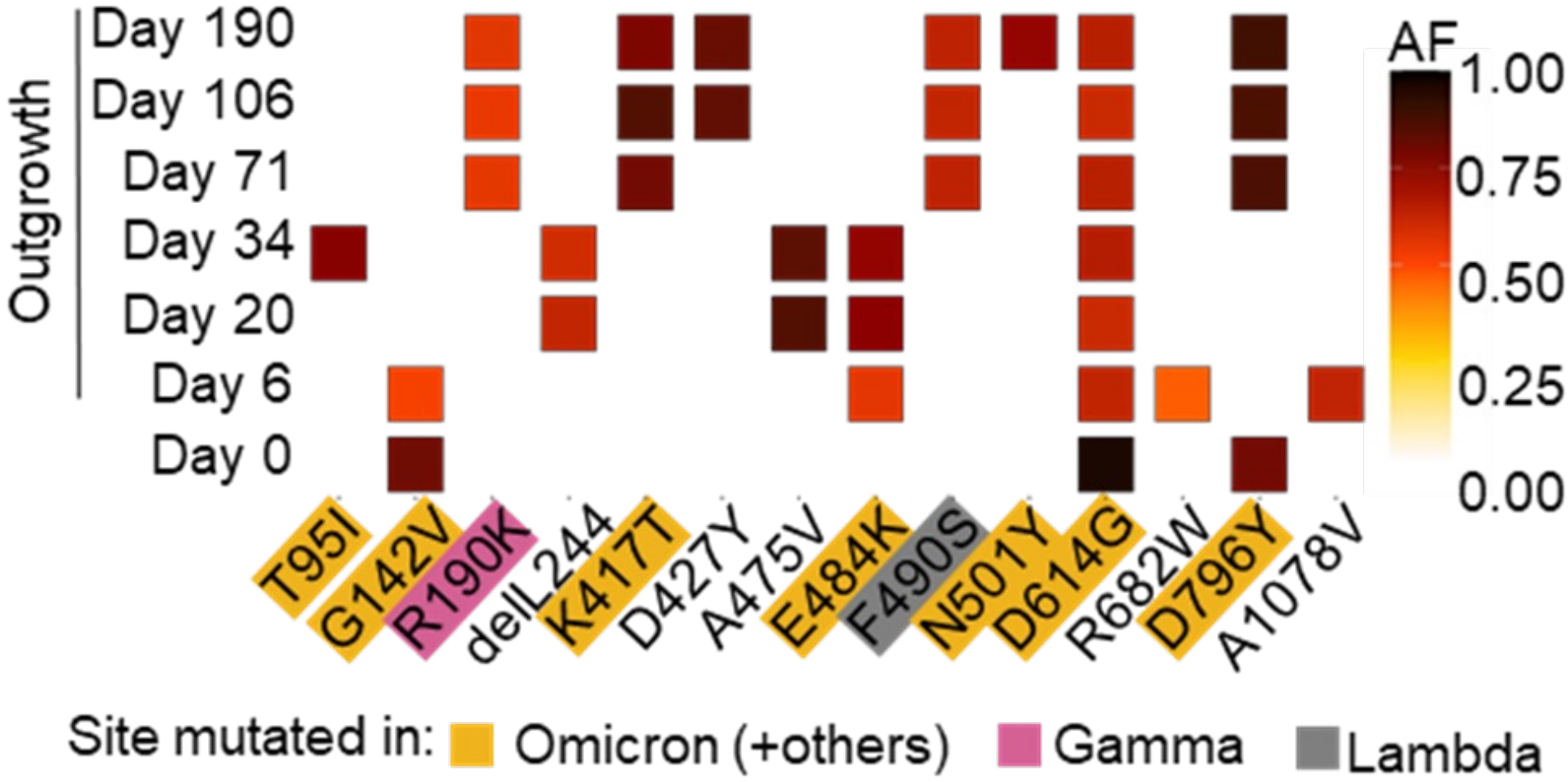


# Long-term infection led to extensive substitutions and deletions in spike and other viral genes

Participant 27 viral isolates elative to B.1.1.273 ancestral virus

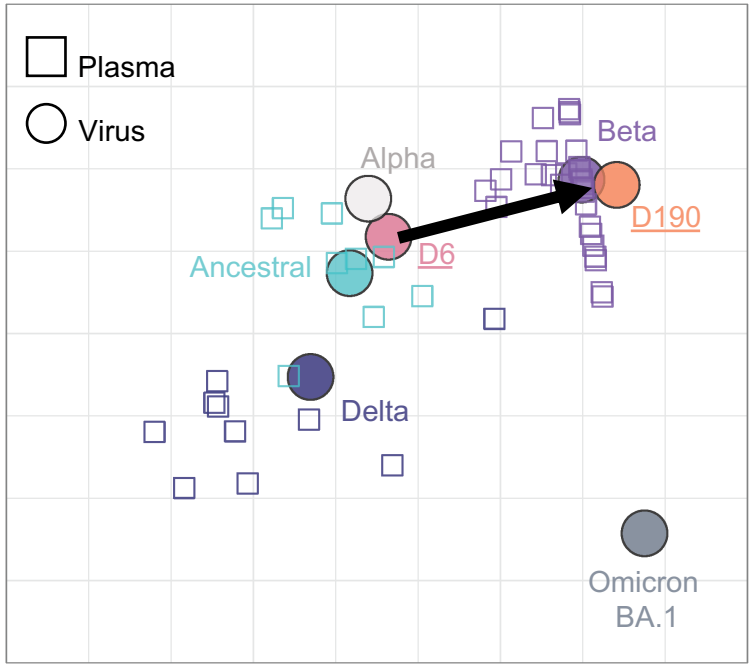


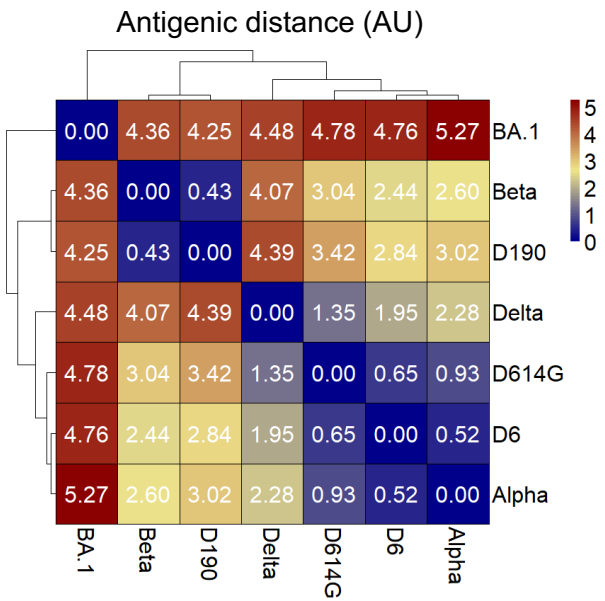
# Many of the spike mutations appearing in variants also appear in immunosuppression

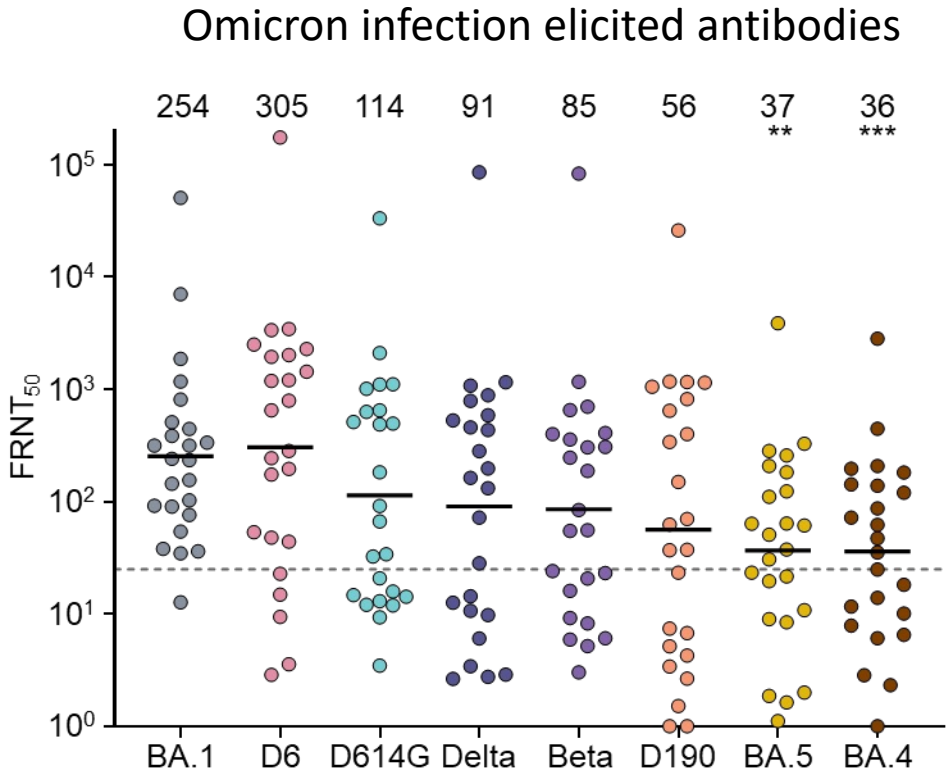



Cele…Sigal, *Cell Host Microbe 2022 30(2):154-162*

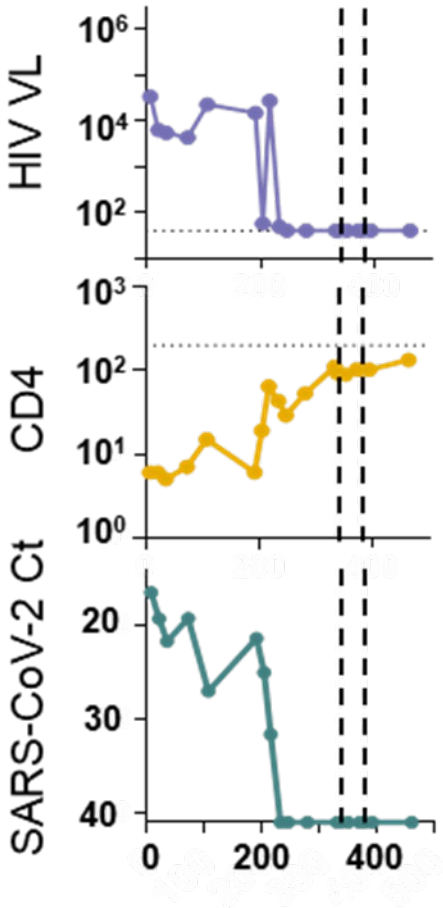
# Evolution of extensive escape from ancestral and Delta variants but less from Omicron

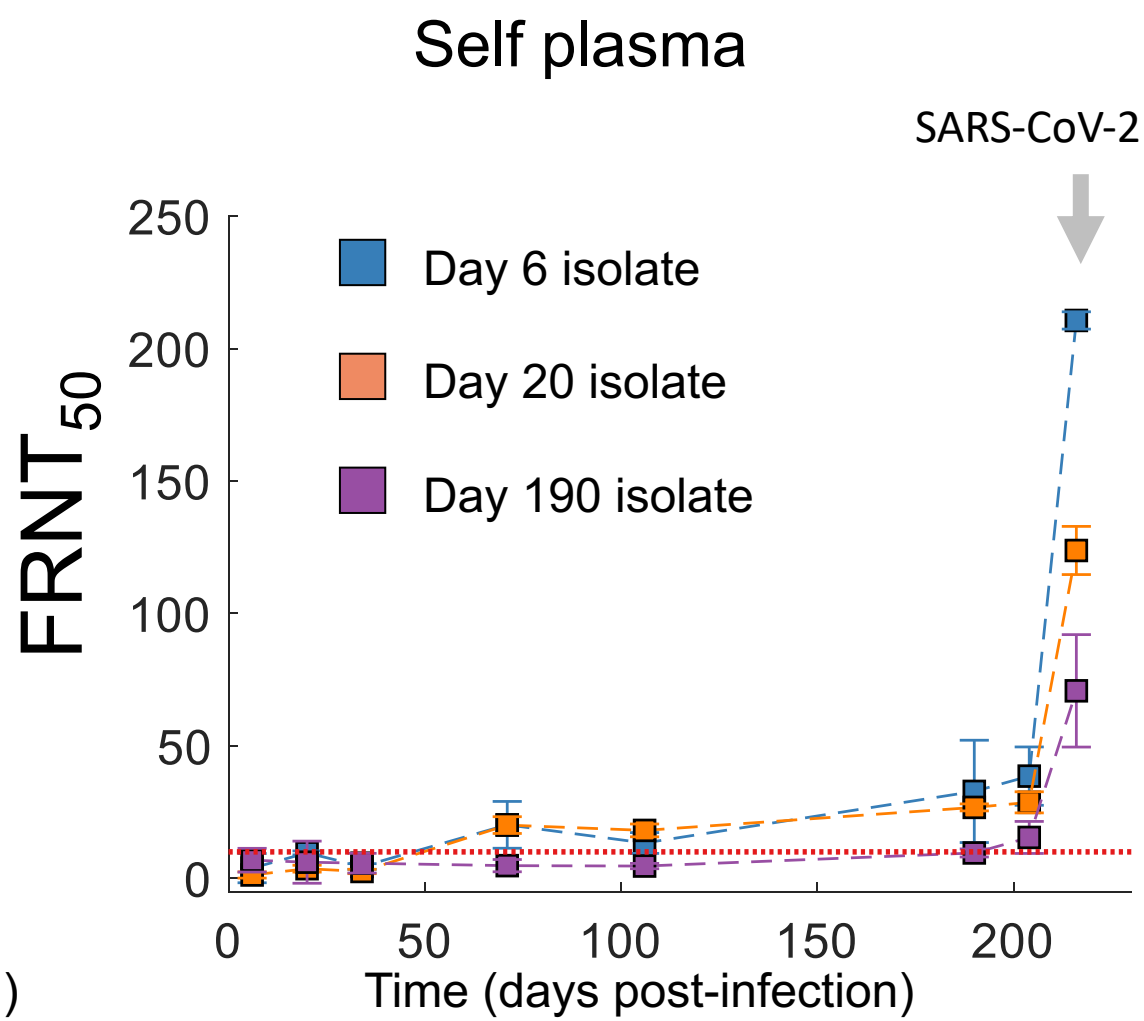


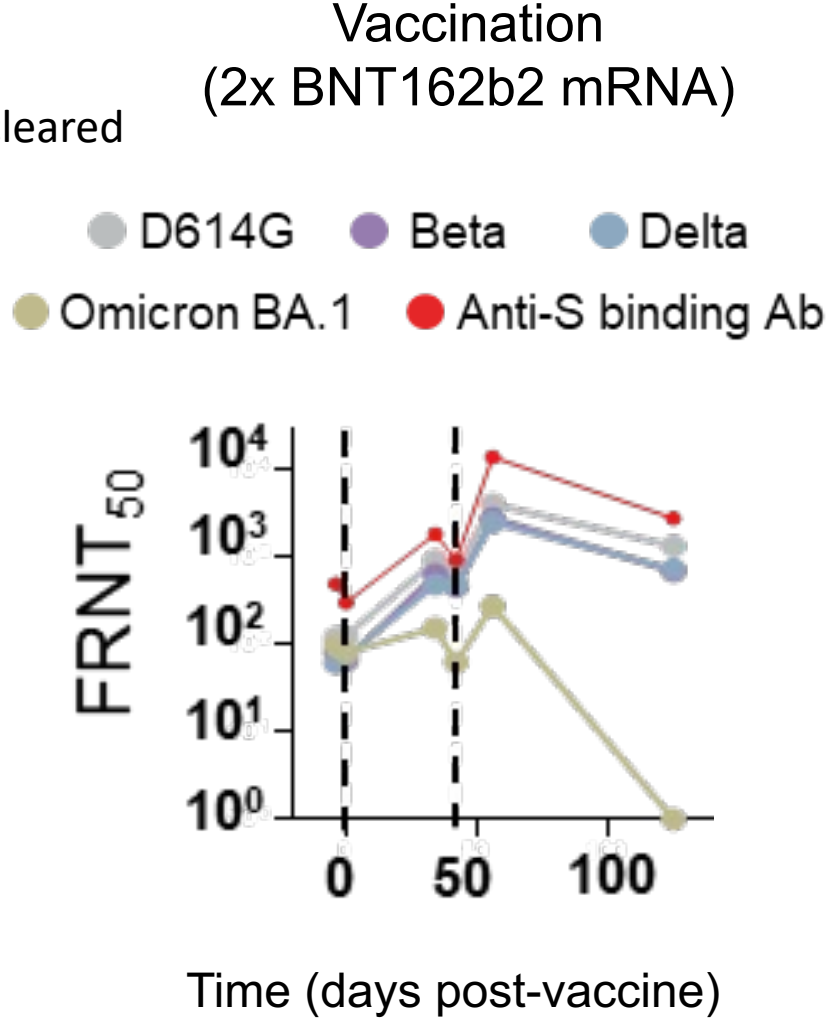



# SARS-CoV-2 clearance closely associated with HIV suppression and gain of neutralizing antibodies



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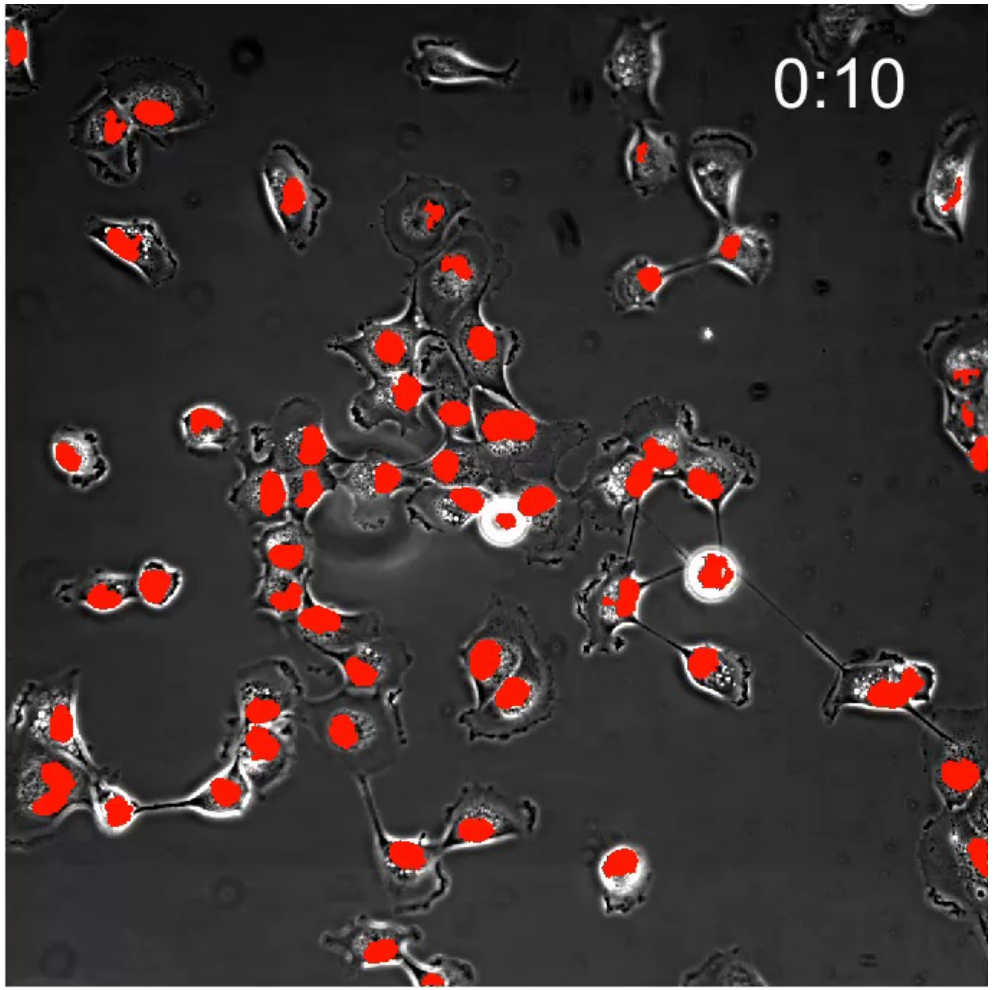
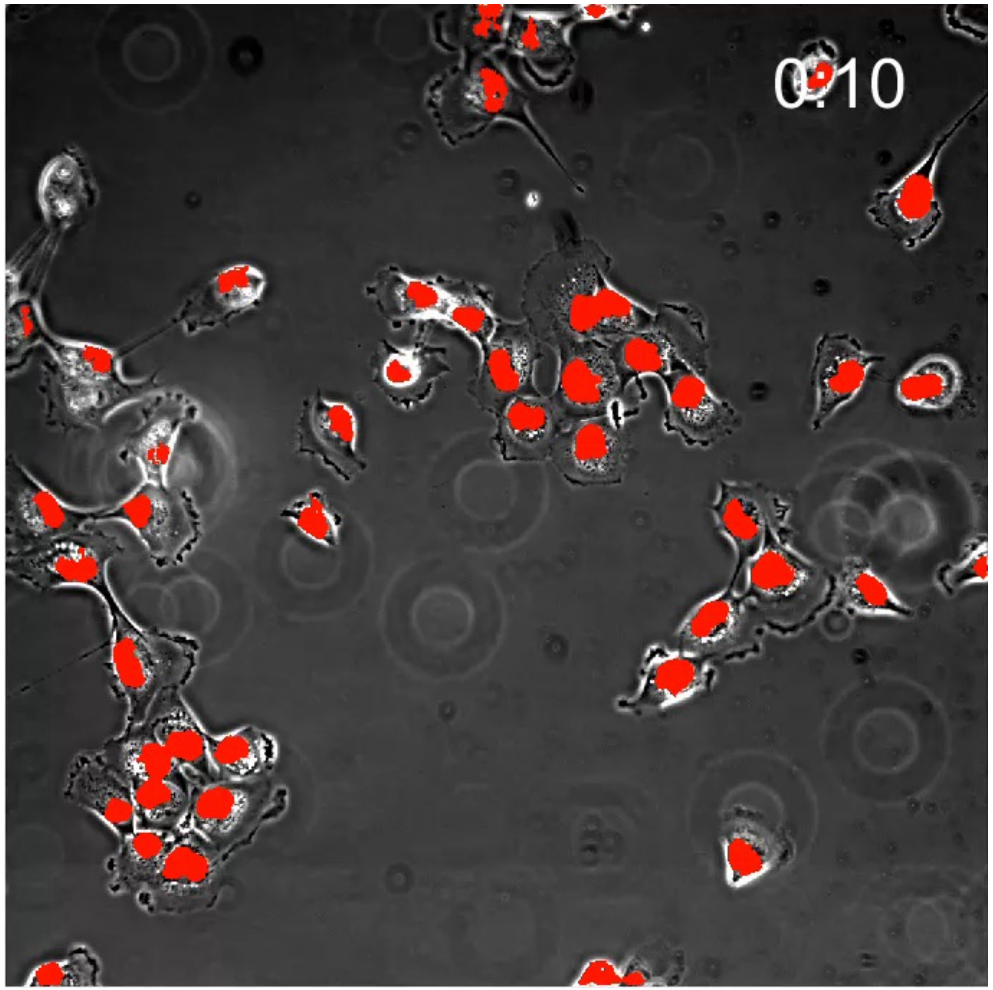
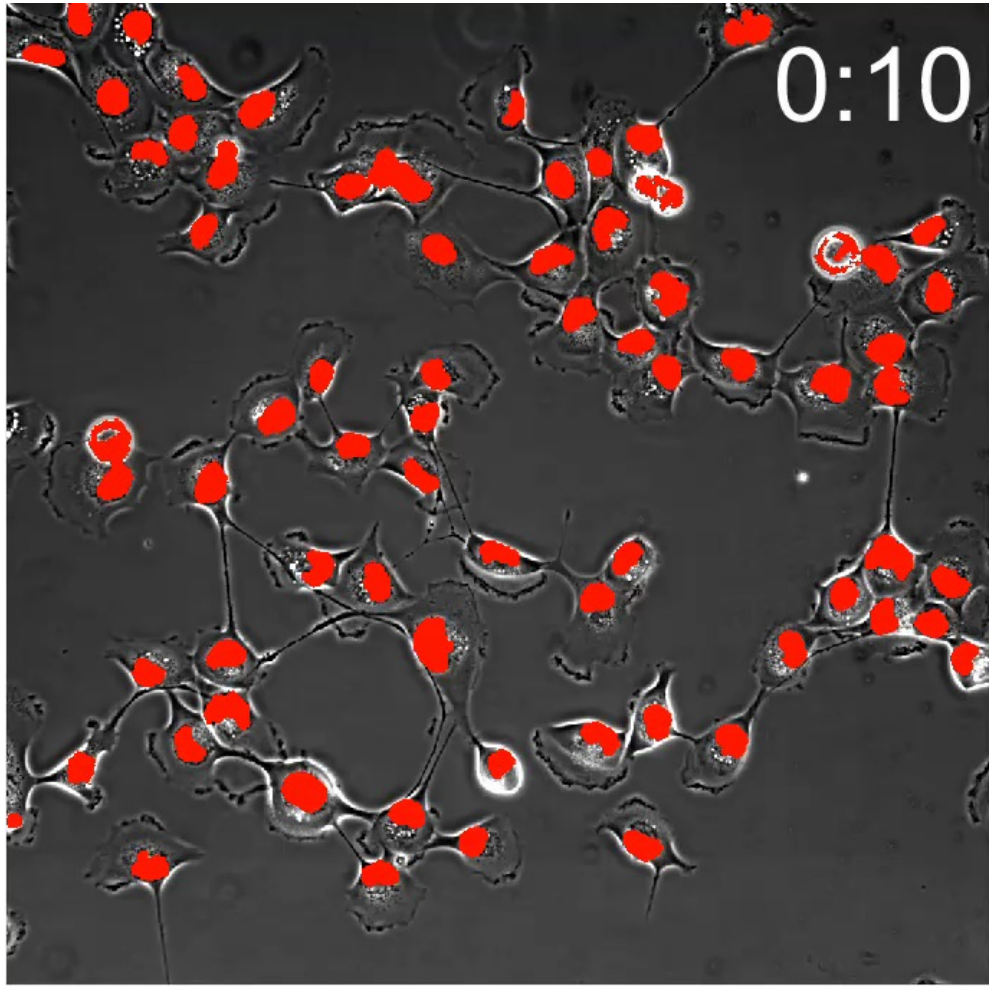
## Uninfected H1299-ACE2 cells



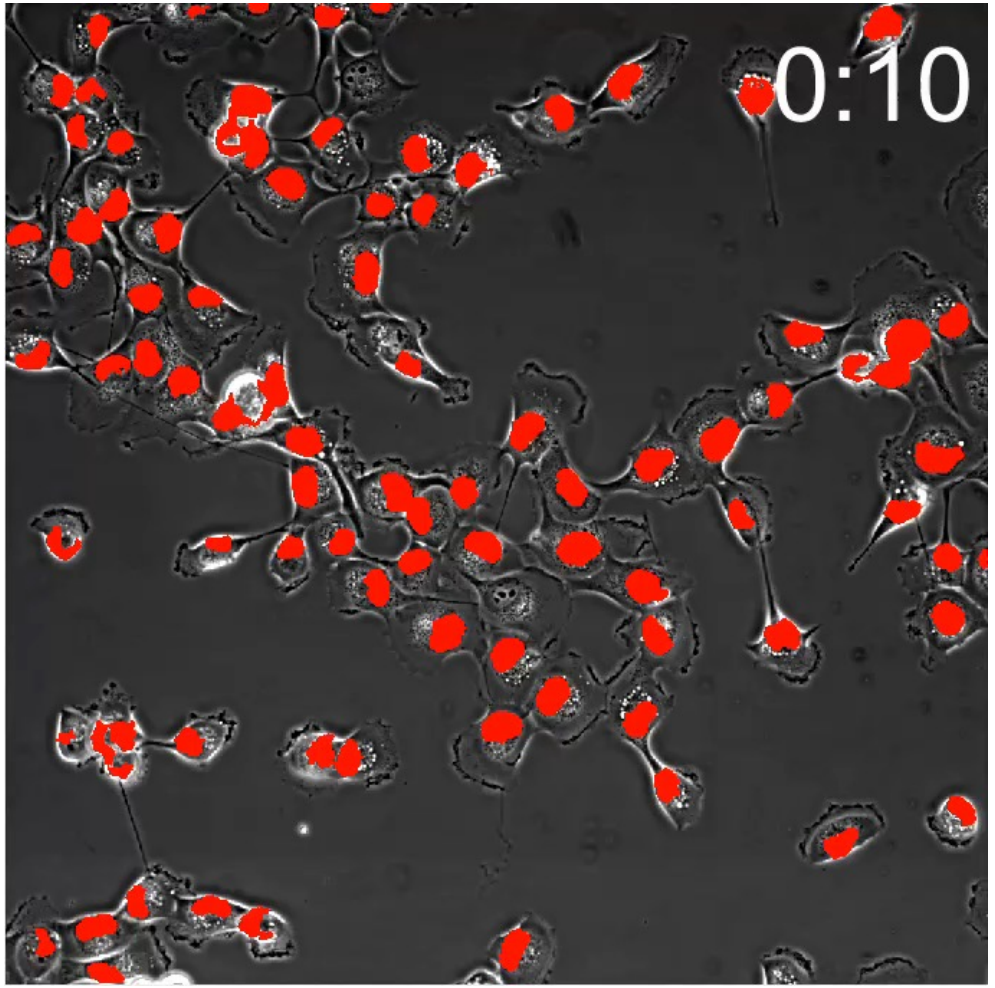

## D614G infected H1299-ACE2 cells



## Day 6 isolate




## Day 190 isolate



# Conclusions

- SARS-CoV-2 long-term infection and evolution is common in people with advanced HIV disease with unsuppressed HIV viremia
- Like variants, evolved SARS-CoV-2 in advanced HIV disease may escape neutralizing immunity
- SARS-CoV-2 may evolve increased pathogenicity through fusion
- This process may be the mechanism SARS-CoV-2 variants are formed.  In could potentially play a similar role in other infections

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