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The interactions between COVID-19, HIV and TB: effect on viral evolution



science & innovation

Department:
Science and Innovation
REPUBLIC OF SOUTH AFRICA

Richard Lessells
14 March 2022



EDGEWOOD CAMPUS



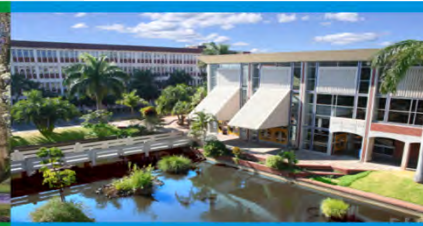
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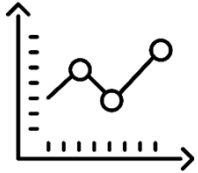
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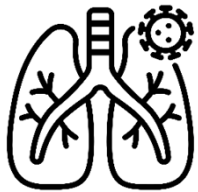
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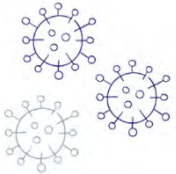
Outline



SARS-CoV-2 virus dynamics may be different in people with advanced uncontrolled HIV



Chronic SARS-CoV-2 infection with intra-host evolution has been reported in the context of advanced HIV

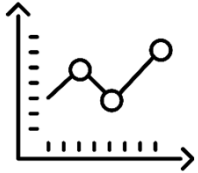


Chronic infection in immunocompromised individuals may be one mechanism for the emergence of novel SARS-CoV-2 variants

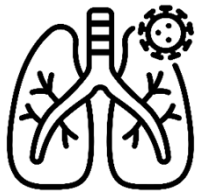


Long-term public health response needs to address these intersecting pandemics

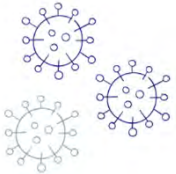
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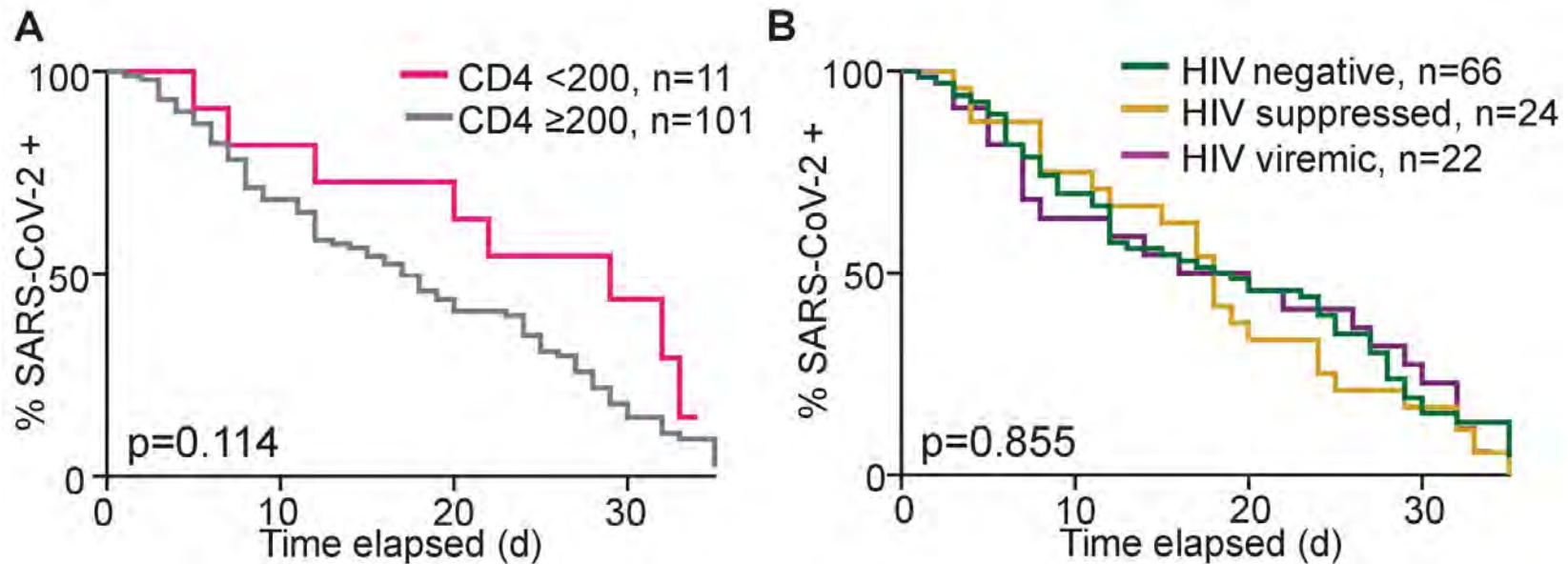
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SARS-CoV-2 virus dynamics

COMMIT-KZN cohort study – hospitalised cases

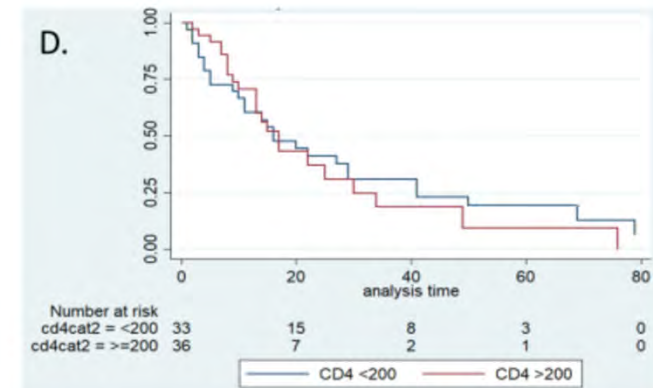
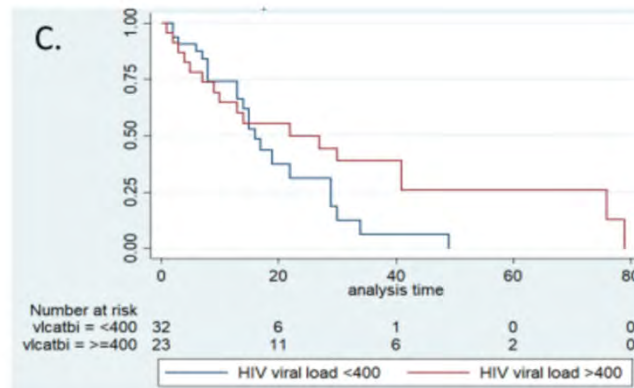
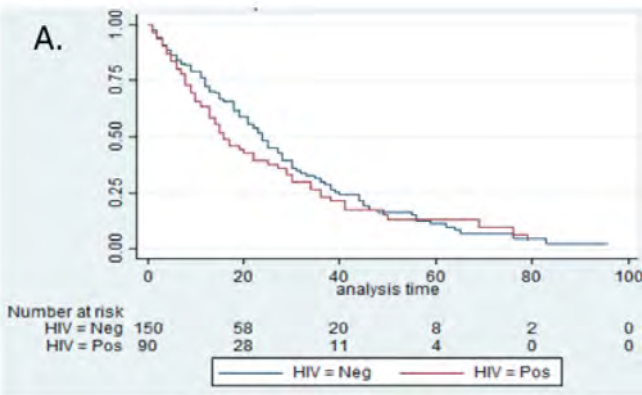


No difference in time to SARS-CoV-2 clearance by HIV status or viraemia; weak evidence of longer time to clearance with CD4+ count <200 cells/ μ L

Karim F, *et al.* eLife 2021

SARS-CoV-2 virus dynamics

NICD COVID-19 shedding study – hospitalised cases

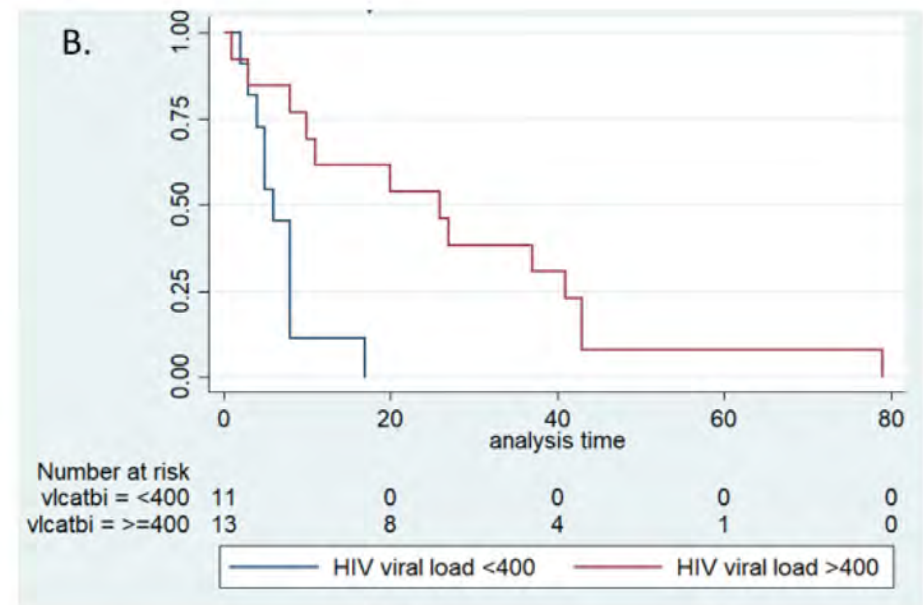
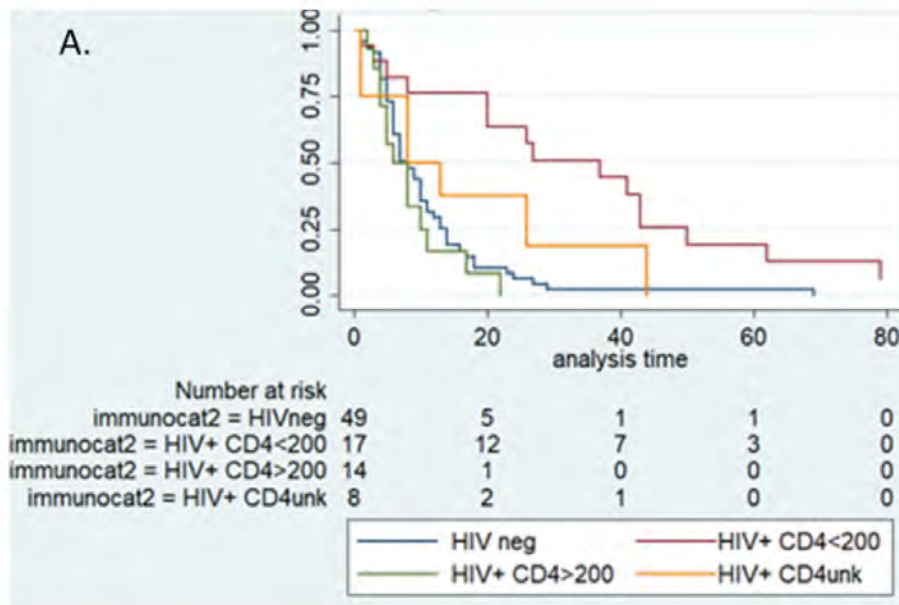


In whole study population, no difference in duration of shedding by HIV status; in PLWH, no significant difference by viral load or CD4+ count

Meiring S, *et al.* CID 2022

SARS-CoV-2 virus dynamics

NICD COVID-19 shedding study – hospitalised cases



In a subset with N-gene Ct value <30 at enrolment, duration of shedding longer with CD4+ <200 cells/ μ L and with VL >400 copies/mL

Meiring S, *et al.* CID 2022

SARS-CoV-2 virus dynamics

PHIRST-C study – community cases

	n	Mean ± SD	Range
Uninfected	608	11.3 ± 7.5	4-60
Infected <400 copies/mL	87	11.7 ± 7.3	4-52
Infected ≥400 copies/mL	22	18.5 ± 26.6	4-137
HIV ± VL unknown	32	8.9 ± 5.6	4-33

	n	Mean ± SD	Range
Uninfected	608	11.3 ± 7.5	4-60
Infected ≥200 cells/μL	99	11.9 ± 8.4	4-52
Infected <200 cells/μL	8	30.2 ± 43.5	4-137
HIV ± CD4 count unknown	34	9.2	4-33

Evidence of longer SARS-CoV-2 shedding in PLWH with viraemia or with CD4 <200 cells/μL (but small numbers)

In multivariable analysis, VL ≥400 copies/mL associated with longer duration of SARS-CoV-2 shedding

Cohen C, *et al.* medRxiv 2021

SARS-CoV-2 virus dynamics

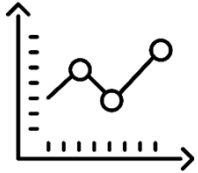
CAP228 study – predominantly outpatient cases

SARS-CoV-2 virus dynamics

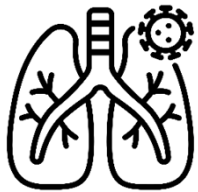
Summary

- Evidence from four independent South African datasets that viraemia and/or low CD4+ counts in PLWH may be associated with persistent SARS-CoV-2 infection
- All studies limited by relatively small numbers of participants with advanced disease
- Interactions with TB infection/disease not well characterized
- Precise definition of population at risk of persistent SARS-CoV-2 infection not yet possible

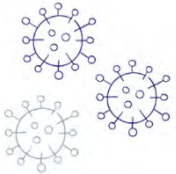
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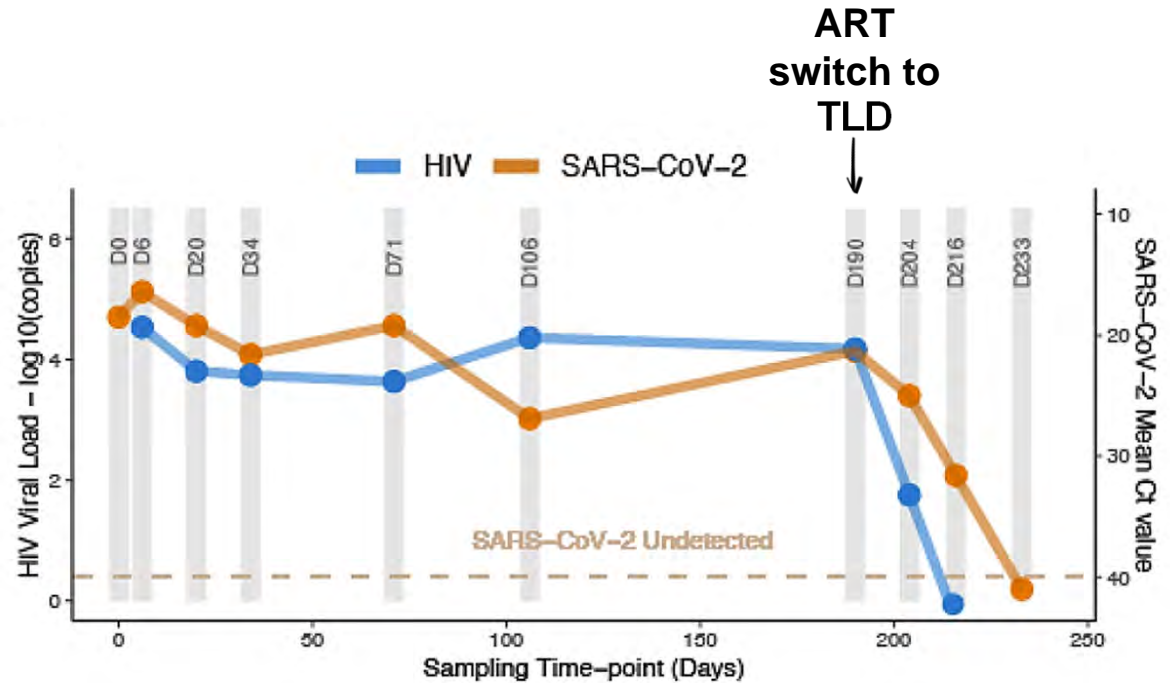
Chronic infection in immunocompromised individuals may be one mechanism for the emergence of novel SARS-CoV-2 variants



Long-term public health response needs to address these intersecting pandemics

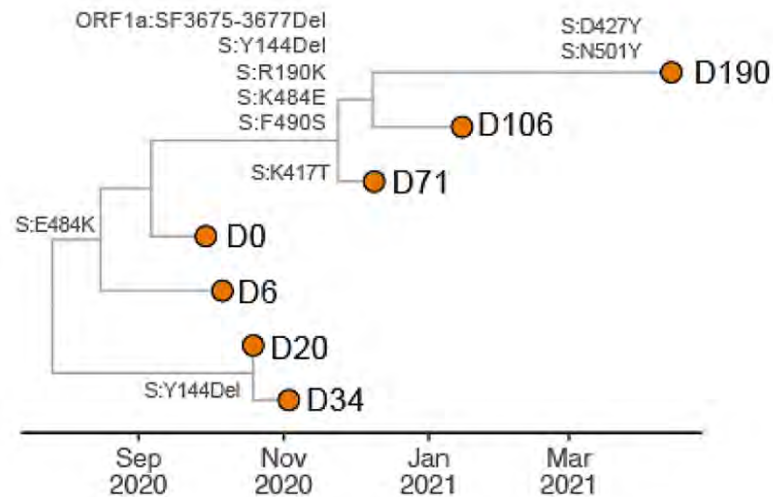
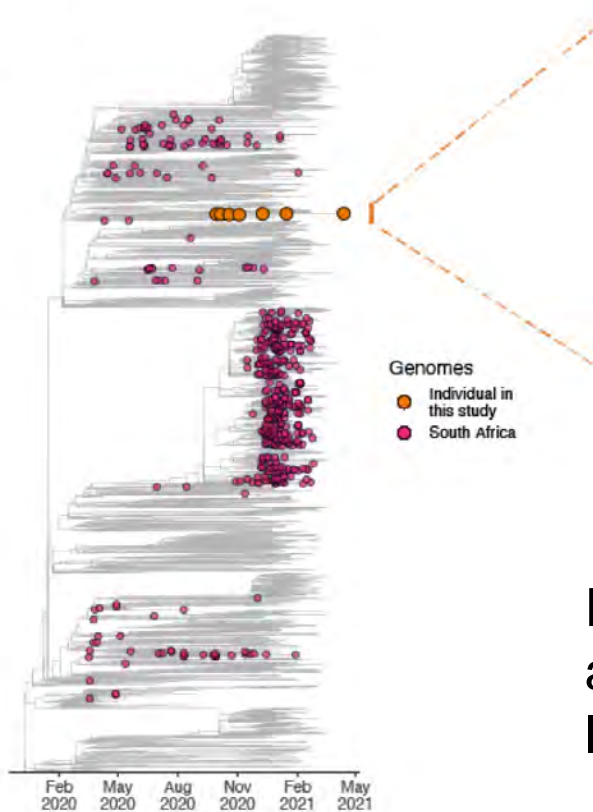
Case report: chronic SARS-CoV-2 infection

- 36-year-old HIV-positive female on TDF/FTC/EFV
- Recurrent cycling in and out of HIV care
- CD4 count 6 cells/ μ L
- Viral load 34,151 copies/mL
- Hospitalised with COVID-19 (oxygen/steroids) – recruited into COMMIT-KZN cohort
- Asymptomatic throughout further follow-up
- Delay in switching ART



Karim F, et al. medRxiv 2021

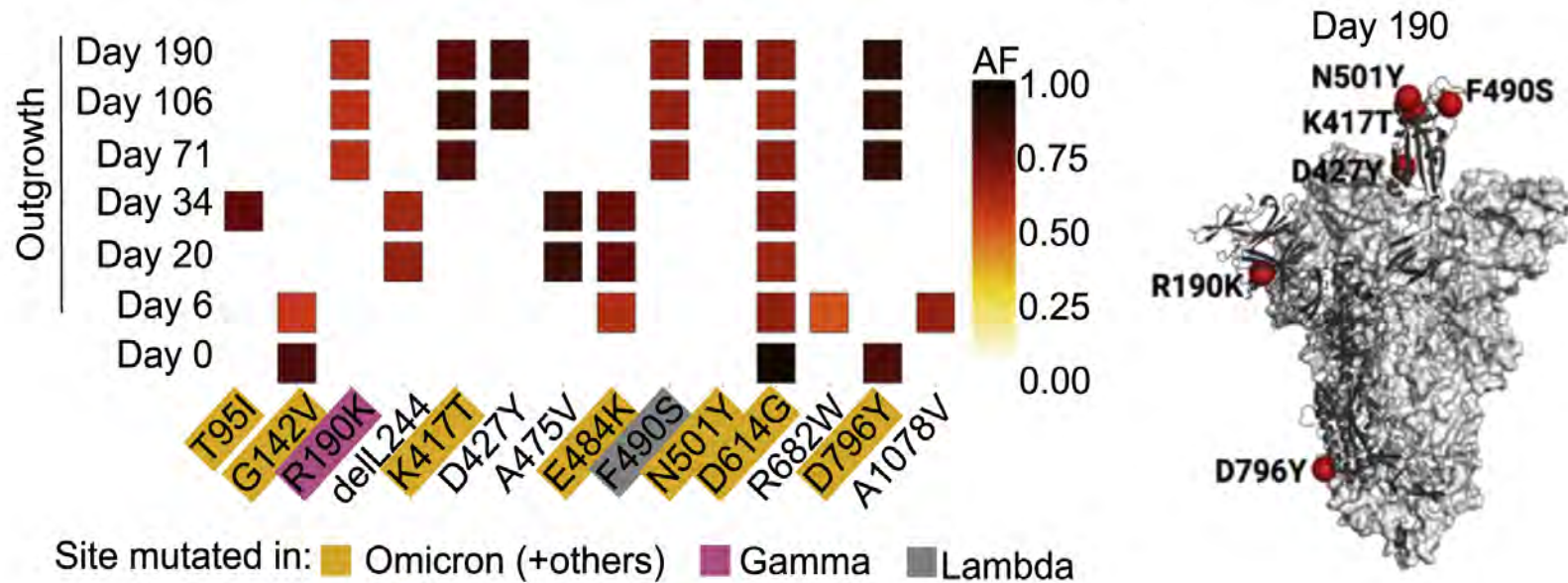
Chronic infection supported by phylogenetic analysis



Phylogenetic analysis supportive of chronic infection as opposed to re-infection with different SARS-CoV-2 lineages

Karim F, *et al.* medRxiv 2021

Spike mutation profile during chronic infection

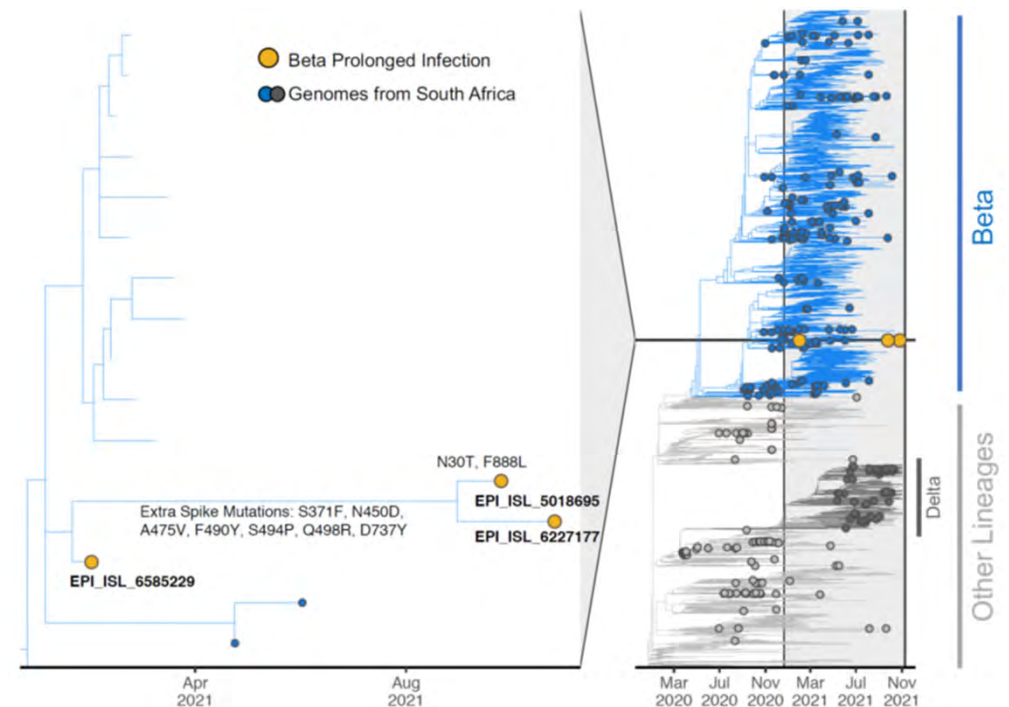


Dynamic shifts in viral population during chronic infection – emergence of mutations associated with escape from different classes of neutralizing antibodies

Cele S, *et al.* Cell Host Microbe 2021

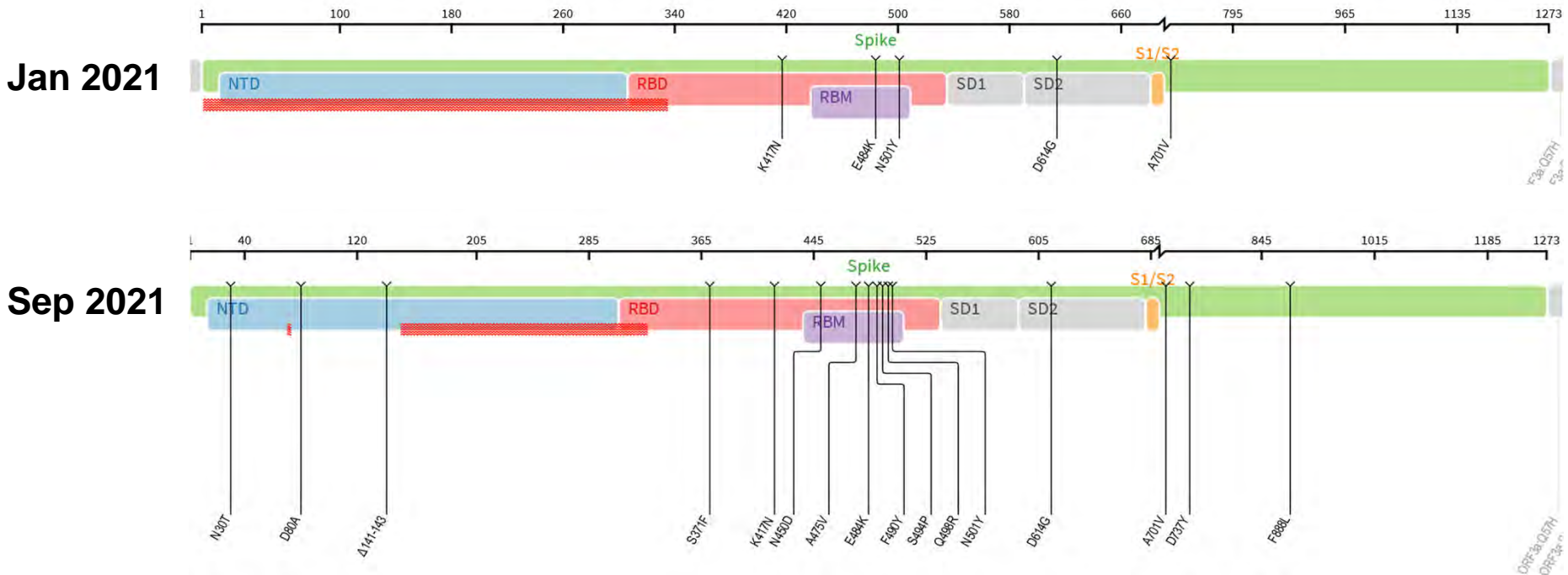
Case report: chronic SARS-CoV-2 infection

- 22-year-old HIV-positive female on TDF/FTC/EFV
- Admitted to hospital Sep 2021 with complications of advanced HIV
- CD4 count 9 cells/ μ L
- Viral load 40,212 copies/mL
- SARS-CoV-2 PCR positive (Ct 16)
- Discovered previous positive PCR Jan 2021
- Sequencing and phylogenetic analysis suggested chronic beta variant infection



Maponga T, *et al.* SSRN preprint 2022

Spike mutation profile during chronic infection



Similar emergence of mutations associated with escape from different classes of neutralizing antibodies; many common to variants of concern

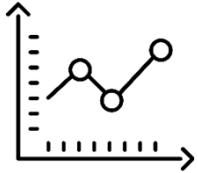
Maponga T, *et al.* SSRN preprint 2022

Chronic SARS-CoV-2 infection in PLWH

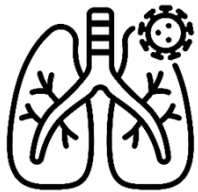
Summary

- Two well-characterized cases of chronic SARS-CoV-2 infection in PLWH with very low CD4+ counts
- Both cases notable for predominantly asymptomatic course – highlights challenges for identification of chronic infections
- In both cases, SARS-CoV-2 clearance followed soon after introduction of effective ART
- Spike mutations predominantly associated with neutralizing antibody escape and/or hACE2 affinity – recurrent mutations observed in these two cases (e.g. 475, 490) despite different infecting lineage

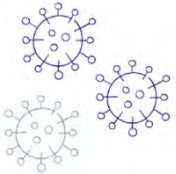
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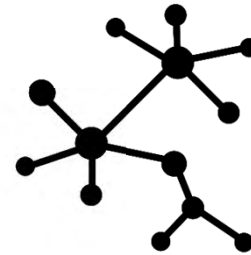
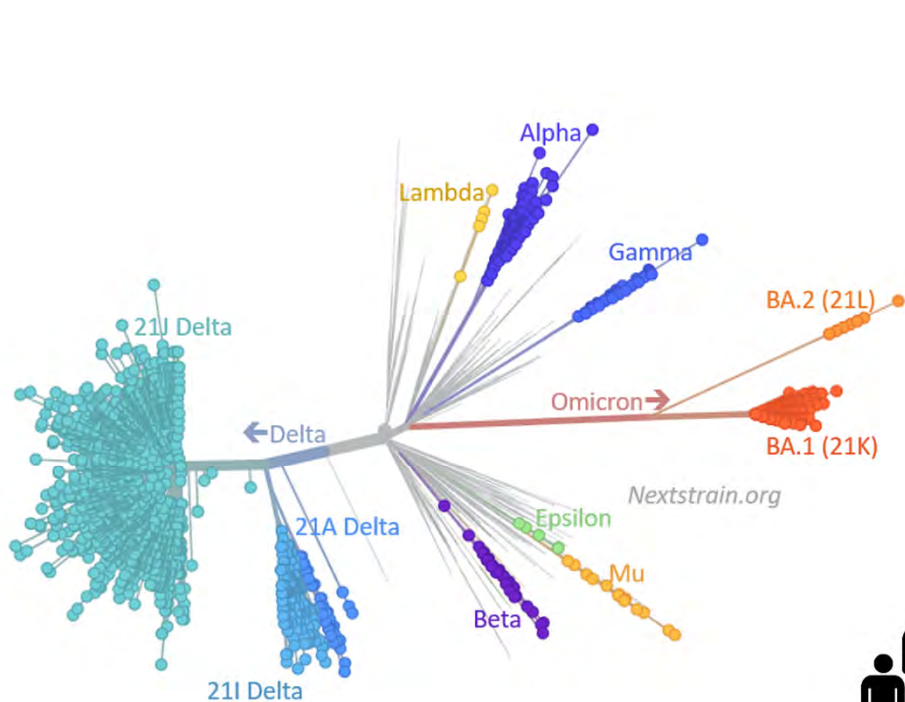


Chronic infection in immunocompromised individuals may be one mechanism for the emergence of novel SARS-CoV-2 variants



Long-term public health response needs to address these intersecting pandemics

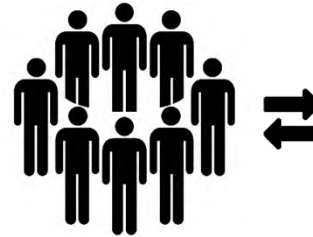
Postulated mechanisms for emergence of SARS-CoV-2 variants of concern



'Silent' evolution through person-to-person spread (genomic surveillance blindspot)



Chronic human infection with intra-host evolution

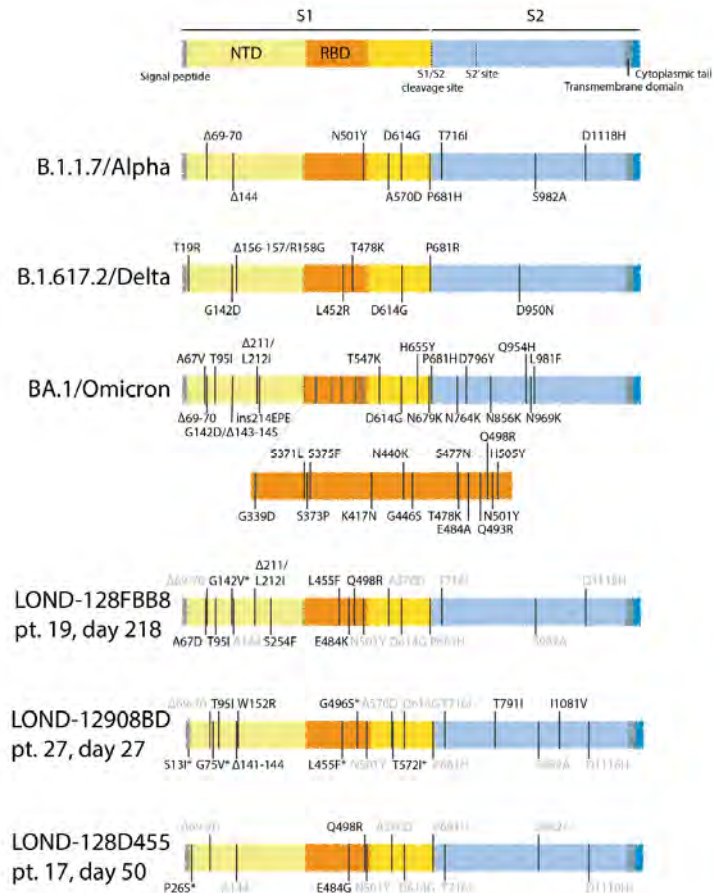


Reverse zoonosis and evolution in animal reservoir, with spillover back to humans

Recurrent mutations in chronic SARS-CoV-2 infections

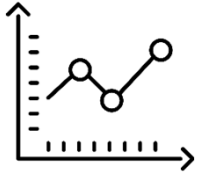
Certain mutations associated with variants of concern have been observed to emerge recurrently in cases of chronic infection

Most recurrent mutations in immunocompromised individuals are associated with hACE2 affinity, immune escape, or viral packaging optimisation

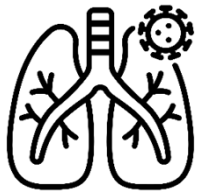


Wilkinson SAJ, *et al.* medRxiv 2022

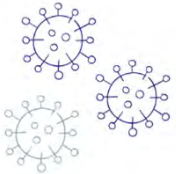
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Implications for public health response

Comment



People in Mombasa, Kenya, hold empty boxes of antiretrovirals in an April protest over drug shortages caused by the COVID-19 pandemic.

Africa: tackle HIV and COVID-19 together

Nokukhanya Msomi, Richard Lessells, Koleka Mlisana & Tulio de Oliveira

Failure to get COVID-19 vaccines to nations with high rates of uncontrolled advanced HIV puts people living with that virus at even greater risk, and could drive the emergence of coronavirus variants.

As scientists and clinical practitioners working in hospitals and laboratories across South Africa, we've seen at first hand the devastation that COVID-19 has brought to the country. Many of our colleagues (including leading scientists and health-care professionals) have died. We have also seen how much harder it has become for people with HIV to get treatment and monitoring, which has meant more people being admitted to hospital with serious illnesses such as tuberculosis and cryptococcal meningitis.

As the world shifts gear in the COVID-19 pandemic – from tackling the immediate crisis to a long-term public health response – we urge governments, health ministries, researchers and other stakeholders worldwide to devote more of their resources and attention

to the interactions between COVID-19 and HIV. Various studies from before the rollout of COVID-19 vaccines show that people with HIV are 30–50% more likely to die from COVID-19. What's more, a failure to tackle the pandemic with sufficient urgency in countries with high rates of uncontrolled advanced HIV could lead to the emergence of variants of the coronavirus SARS-CoV-2 that spread more easily between people or render the vaccines less effective. Conversely, both diseases could be curbed more effectively if they are tackled simultaneously, with public health responses strengthened by the lessons learnt from both.

Risk analysis
In 2020, the World Health Organization (WHO) created a platform for standardized clinical data obtained from people with suspected or

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- May need enhanced monitoring/surveillance for chronic infections in people with advanced HIV
- Intensify efforts to strengthen HIV care cascade to optimize viral suppression
- Integration of COVID-19 vaccination into HIV services to ensure full vaccination of priority groups
- Address research gaps, e.g.
 - Mechanisms of virus evolution in chronic infection
 - Risk of chronic infection post-vaccination and in re-infections
 - Role of therapeutic agents (antivirals, monoclonal Abs) in chronic infection

Msomi N, *et al.* Nature 2021

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NGS-SA team involving NHLS, NICD, UCT, Stellenbosch University, University of Free State, University of Pretoria

COMMIT-KZN team involving AHRI, KRISP, UKZN, CAPRISA, Oxford University, UCL

SA variant consortium involving multiple individuals/groups

Funders including DSI, SAMRC, BMGF

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