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

Richard Lessells
14 March 2022
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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Long-term public health response needs to address these intersecting pandemics
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/µL

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/µL and with VL >400 copies/mL

Meiring S, et al. CID 2022
### SARS-CoV-2 virus dynamics

**PHIRST-C study – community cases**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected</td>
<td>608</td>
<td>11.3 ± 7.5</td>
<td>4-60</td>
</tr>
<tr>
<td>Infected &lt;400 copies/mL</td>
<td>87</td>
<td>11.7 ± 7.3</td>
<td>4-52</td>
</tr>
<tr>
<td>Infected ≥400 copies/mL</td>
<td>22</td>
<td>18.5 ± 26.6</td>
<td>4-137</td>
</tr>
<tr>
<td>HIV ± VL unknown</td>
<td>32</td>
<td>8.9 ± 5.6</td>
<td>4-33</td>
</tr>
</tbody>
</table>

### 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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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/µL
- 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/µL
- 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
Outline

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

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

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

4. 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

- 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


UKZN INSPIRING GREATNESS
Acknowledgements

**Krisp/Ceri:** Tulio de Oliveira, Houriiyah Tegally, Eduan Wilkinson, Emmanuel James San, Jennifer Giandhari, Sureshnee Pillay, Yeshnee Naidoo, Monika Moir, Stephanie van Wyk, Lavanya Singh, Upasana Ramphal, Yajna Ramphal

**Ahri:** Alex Sigal, Farina Karim, Sandile Cele, Khadija Khan, Dirhona Ramjit, Mallory Bernstein, Willem Hanekom

**Ukzn:** Yunus Moosa, Bernadette Gosnell

**Stellenbosch University:** Wolfgang Preiser, Tongai Maponga, Montenique Jeffries, Andrew Sutherland, Gert van Zyl

**Caprisa:** Kogie Naidoo, Aida Sivro

**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
References


Karim F, et al. Persistent SARS-CoV-2 infection and intra-host evolution in association with advanced HIV infection. medRxiv 2021 Jun 4


Maponga TG, et al. Persistent SARS-CoV-2 infection with accumulation of mutations in a patient with poorly controlled HIV infection. SSRN 2022 Jan 21
