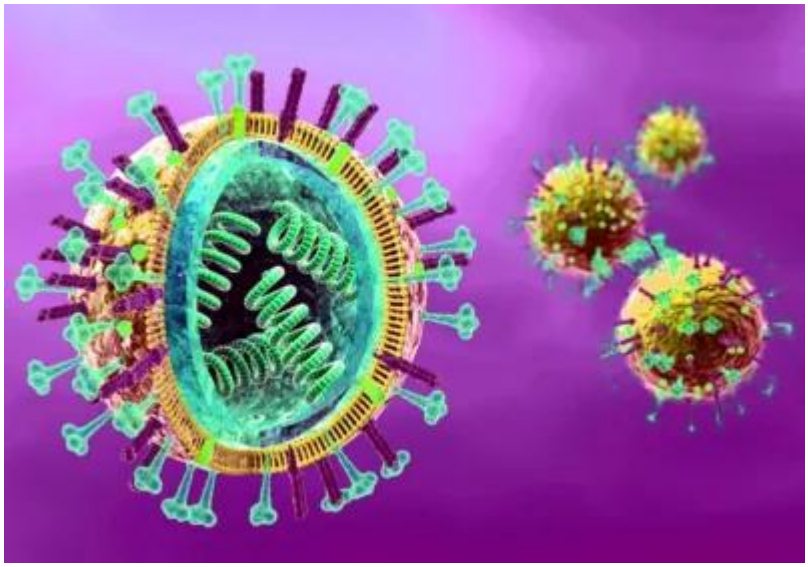
Several studies have suggested that genetic variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerge preferentially in immunocompromised individuals. As the processes underlying the intra-host evolution are not fully understood, a group of scientists from the United States, South Africa, and Canada used longitudinal sample sets from individuals infected with the human immunodeficiency virus (HIV) to investigate the evolution of SARS-CoV-2 during persistent infection. In previous studies, new SARS-CoV-2 mutations have typically been detected in individuals infected with HIV weeks or months after the COVID-19 onset, showing a temporal threshold after which the virus accumulates sufficient mutations to evolve within an individual.

Although the advanced approaches to defining intra-host genetic diversity of the virus have not been widely used, the authors emphasized that the extent, kinetics, and patterns of SARS-CoV-2 diversification in immunocompromised individuals are crucial to be defined to understand the biology of persistent infections and the emergence of new variants of concern (VOCs).

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein.



About the study

Researchers developed a high-throughput, single-genome amplification and sequencing

(HT-SGS) methodology to obtain gene sequences of the SARS-CoV-2 S protein from upper respiratory tract samples in two groups: 22 individuals infected with HIV and 25 without HIV.

A group of 22 individuals infected with HIV was divided into a cohort hospitalized for advanced HIV (n=18) and an outpatient cohort (n=4). In the group of hospitalized HIV patients, ten had advanced HIV infection, defined by peripheral blood CD4 T-cell count below 200 cells/μL, five did not have available CD4 count, and three had CD4 counts ≥200 cells/μL. From the outpatient cohort, two HIV patients had CD4 counts below 200 cells/μL, and two HIV patients had CD4 counts ≥200 cells/μL.

Upper respiratory tract samples were taken from study participants at the time of study enrollment, at a median of four days after the onset of COVID-19 symptoms, and every second day (hospitalized cohort) or three times weekly (outpatient cohort), until the cessation of SARS-CoV-2 RNA shedding.

Results

Using HT-SGS methodology researchers obtained up to ~103 gene sequences of the SARS-CoV-2 S protein from each of 184 respiratory samples from the 47 study participants, which resulted in 70,968 single-genome sequences from individuals with HIV and 29,824 single-genome sequences from individuals without HIV.

The results showed that in individuals infected with HIV who had CD4 T-cell counts ≥200 cells/μL and individuals who did not have HIV, the majority of single-genome sequences of the SARS-CoV-2 S protein in each individual matched one haplotype that predominated throughout the infection. By contrast, individuals with advanced HIV showed increased intra-host diversity of the S protein, with a median of 46 haplotypes *per* person.

Within days of the COVID-19 onset, in individuals with advanced HIV infection the permissiveness for SARS-CoV-2 replication, often accompanied by uncontrolled HIV viremia, was found to be associated with high levels of the S protein genetic diversity. At this time point, the intra-host diversity of the SARS-CoV-2 S protein was significantly higher among HIV patients with advanced infection than in individuals who were not infected. Importantly, higher intra-host diversity of the SARS-CoV-2 S protein observed immediately after the onset of COVID-19 symptoms predicted longer shedding of SARS-CoV-2 RNA.

The composition of the S protein sequences fluctuated rapidly over time in individuals with advanced HIV infection and CD4 T-cell counts below 200 cells/μL. According to the authors,

the evolution of SARS-CoV-2 in individuals with advanced HIV infection is not only a product of random diversification through unchecked replication, but also of intra-host adaptation that may significantly increase the risk for the generation of new VOCs.

Conclusion

These results demonstrated striking differences in intra-host SARS-CoV-2 genetic diversity and evolution between individuals with advanced, poorly controlled HIV infection and those with controlled infection or without HIV. A remarkable intra-host genetic diversity of SARS-CoV-2 in patients with advanced HIV infection suggests that adaptive intra-host SARS-CoV-2 evolution may contribute to the emergence of new VOCs. The authors concluded that further research is required to examine whether intra-host SARS-CoV-2 variants that arise in individuals with HIV or other immunocompromising conditions differ in their potential to evade pre-existing immunity in immunocompetent individuals.

This study has been published on a preprint server and is currently being peer-reviewed.

Journal Reference

Hee Ko S, Radecki P, Belinky F et al. Rapid Emergence and Evolution of SARS-CoV-2 Variants in Advanced HIV Infection. bioRxiv preprint
https://doi.org/10.1101/2024.01.05.574420