Expanding Efforts and Support to Respond to the HIV and COVID-19 Intersecting Pandemics

Considerable inferential data indicate that immunocompromised persons with persistent COVID-19 infection may be involved in the generation of SARS-CoV-2 variants of concern globally.\(^1\)\(^2\) The largest immunocompromised population worldwide is people living with HIV. Although tremendous gains have been made in providing access to lifesaving antiretroviral therapy, only approximately 50% of the estimated 37.7 million people living with HIV globally are optimally treated.\(^3\) The emergence of the SARS-CoV-2 Omicron variant is a stark illustration of the intersecting COVID-19 and HIV pandemics, highlighting the interrelationships and detrimental effects each of these infectious diseases has on the other.\(^4\) HIV infection is a risk factor for increased mortality from COVID-19, even more so when HIV is not controlled by antiretroviral therapy.\(^5\) and emerging data suggest that immunosuppression may be facilitating the development of SARS-CoV-2 variants of concern.\(^1\)\(^3\) Sub-Saharan Africa has the largest global HIV epidemic with as many as 1 in 5 adults having chronic HIV.\(^5\) In the US, an estimated 3 to 4 million persons live with immunocompromising conditions, and an additional estimated 22 million individuals with autoimmune or inflammatory conditions may receive immunosuppressive therapies, representing approximately 8% of the population. Thus, proportionally, southern Africa has a significantly higher prevalence of immunocompromised persons. In addition, households and densely populated communities in Africa are much more frequently populated with immunosuppressed individuals living in close proximity than in the US and Europe. Local and national level health services have been adversely affected by both lockdown strategies and already scarce personnel and resources that have been diverted from HIV and tuberculosis programs to respond to COVID-19. HIV testing has been particularly affected, meaning more people are living with undiagnosed HIV infection and subsequent immune compromise and untreated tuberculosis. Adequate HIV therapy appears necessary for detectable immune responses to COVID-19 vaccination.\(^3\) Tuberculosis complications and worsens COVID-19 care. COVID-19 vaccine coverage in Sub-Saharan Africa remains remarkably low, estimated at 10% to 20%, with no programmatic emphasis to reach people living with HIV.

Multistep stable mutational changes (saltational evolution) seen with the major SARS-CoV-2 variants have been reported exclusively in immunocompromised persons; with immunocompetent persons exhibiting limited within-host strain diversity.\(^7\) Three times over the past year, new lineage variants with novel mutational and epidemiological properties have emerged (Alpha, Beta, and now Omicron) and these new lineage variants with both increased transmissibility and now high immune escape potential undermining the current best efforts at pandemic control.\(^1\)\(^3\)

Even though the genesis of such variants is incompletely understood,\(^6\) the related sublineages of the Omicron variant (BA.1, BA.2, and BA.3) provide insight into these intersecting pandemics. The BA.1 variant was first identified in samples from Botswana and South Africa isolated on November 11, 2021, and November 14-16, 2021, respectively. The BA.2 and BA.3 variants were identified shortly thereafter in samples from South Africa on November 17 and November 18, 2021, respectively. The close genetic similarities among these Omicron sublineages suggest a recent shared origin in southern Africa.\(^9\) Omicron lineages also display a complex pattern of shared mutations that strongly suggest recombination among BA.1 and BA.3, with weaker evidence for recombination between BA.1 and BA.2. These data support the concept that the Omicron lineage was derived from the B.1.1 lineage in mid-2020 and acquired its mutational change essentially in situ in a single or very limited number of individuals, rather than through interaction with other circulating variants such as Alpha and Delta.\(^10\) Interlineage recombination requires that highly divergent sublineages replicate simultaneously within a single host cell. Recombination is expected for viral populations evolving within an individual immunosuppressed host; recombination is relatively rare for SARS-CoV-2 lineages in circulation.\(^10\) The high number of mutations that are specific to each Omicron sublineage indicate its progenitor population maintained substantial genetic diversity. Such persistent replication in a microscopic vacuum is an uncommon event, which may have been enhanced by the large reservoir of immunosuppressed persons living in common households capable of allowing persistent replication under low-grade immune selection. Genetic clock predictions that Omicron emerged 6 weeks prior to widespread detection in South Africa\(^9\) makes identification of a patient zero highly improbable. Therefore, although it is not possible to exclude other origins of Omicron such as reverse zoonosis, the available evidence supports within individual evolutionary processes.

This association between COVID-19 variants of concern, high prevalence of immunosuppression, and HIV has several important policy implications (eTable in the Supplement). First, it is imperative to reestablish the HIV diagnosis and care services and integrate COVID-19 vaccination and treatment services for all people living with HIV. This must occur now rather than waiting to have optimal guidelines for managing vaccination and use of other preventive strategies for immunocompromised persons in low- and middle-income countries (LMICs).
There must be a conscious prioritization for COVID-19 surveillance, prevention, and clinical and virological monitoring among immunocompromised persons, especially people living with HIV. This is to improve COVID-19–related outcomes for people living with HIV and also assist countries in managing COVID-19 transmission and the emergence of new variants of concern. Some argue that such emphasis increases stigmatization of HIV infection. Prioritizing care for immunocompromised persons should not be stigmatizing, and stigma mitigation measures can and should be implemented with these enhanced public health and clinical strategies. The main tool to reduce persistent COVID-19 infection is optimal HIV therapy with sustained virological suppression. Increased attention to these issues also could be of direct benefit to people living with HIV, other vulnerable groups, and their communities.

Second, countries with high HIV incidence must be resourced to better identify people living with HIV and ensure easy and well-supported access to and monitoring of antiretroviral therapy. People living with HIV, including those not receiving treatment, need to be prioritized globally for COVID-19 vaccination and booster shots. This requires resources, including increased funding at national levels in LMICs with high population prevalence of immune compromise, and expansion of key donor programs, including the US bilateral President’s Emergency Plan for AIDS Relief (PEPFAR) program and the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM). Expansion of the PEPFAR and GFATM programs could be vital in addressing these intersecting pandemics. Such programs may ensure that many more people living with HIV are identified and have access to antiretroviral therapy and highly efficacious vaccines against COVID-19 (eTable in the Supplement). Regionalization of COVID-19 vaccine manufacturing programs could be linked to these programs.

Third, people living with HIV, especially those with low CD4 counts (<200 cells/μL), must be monitored virologically for persistent COVID-19 infection irrespective of symptoms; those with extended detection of SARS-CoV-2, especially at high titers, need to be identified, their isolates sequenced, and epidemiological measures undertaken to ensure caretakers are vaccinated and monitored for COVID-19. The investigative community must develop clinical trials to test therapeutic interventions for immunosuppressed patients with persistent COVID-19 so that guidelines can then be developed. Clinical issues, such as whether individuals should be vaccinated or whether long-acting monoclonal antibody prophylaxis should be used, require study. Until then, approaches and interventions for individuals who do not respond well to vaccination or acquire breakthrough infections could include development of boosting strategies, making broadly neutralizing monoclonal antibodies available, and improving access to rational use of antivirals, including monitoring for potential antiviral resistance.

The PEPFAR infrastructure, which has been built with African and US partners, coupled with the GFATM funding mechanism, is a highly appropriate foundation for rolling out these efforts. The expansion of these programs must be adequately resourced to respond quickly to the intersecting epidemics. The current approach is costing countries their economies and reversal of sustainable development goals. Billions of dollars lost from reduced travel has affected tourism industries in LMICs. In addition, without control over the emergence of variants of concern, the constant pressure to produce new vaccines and monoclonal antibodies will have international ramifications and effects on revenue, both direct and indirect, and social and psychological health.

The global community cannot expect to achieve pandemic control while the continent of Africa is left unprotected from COVID-19 due to inadequate access to vaccines and therapeutics. Omicron has emphasized this reality yet again. Continuation of current approaches by both Western and African governments must change, and public health responses must be adequately resourced by donors or other sources. African governments also need to increase vaccine coverage, possibly through vaccine mandates and resource health services, to reduce the economic and public health consequences of these intersecting pandemics on their countries and societies.

ARTICLE INFORMATION
Published Online: March 11, 2022.
doi:10.1001/jama.2022.3517

Conflict of Interest Disclosures: Dr Corey reported receiving grants from the National Institute of Allergy and Infectious Diseases during the conduct of the study. Dr Corbett-Detig reported receiving grants from the US Centers for Disease Control and Prevention and the National Institutes of Health (NIH). Dr Beyrer reported serving as senior scientific liaison to the COVID Vaccine Prevention Network and receiving salary support from the NIH during the conduct of the study.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the opinions of the NIH.

Additional Contributions: We thank Carlos Del Rio, MD (Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia), and Glenda Gray, MB BCh (president and CEO, South African Medical Research Council), who were instrumental in the original construction of the manuscript and discussion of its policy implications for the region and Mindy Miner, PhD (Fred Hutchinson Cancer Research Center, University of Washington, Seattle), for assistance with writing and editing. No compensation was provided beyond their regular salaries.

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