The extent of vaccine hesitancy varies by community and type of immunization. Even small increases in parental vaccine hesitancy resulting in undervaccination may lead to outbreaks of vaccine-preventable disease, especially when there are clusters of unvaccinated or undervaccinated children in individual communities.

An audio interview with David Higgins is available at NEJM.org

We believe it will be essential to double down on efforts to increase confidence and trust in vaccines, including in populations that have experienced mistreatment by the medical community. Because of the complexity of this issue, addressing parental vaccine hesitancy requires partnerships among academic experts in various disciplines, community leaders, policymakers, public health professionals, and parents. But these efforts are unlikely to be successful if there is widespread promotion and acceptance of the idea that parental vaccine hesitancy is the norm in the United States. What should be normalized is parents confidently having their children vaccinated: despite all the attention-grabbing misinformation out there, that is still, in fact, the norm.

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From the Adult and Child Center for Outcomes Research and Delivery Science, University of Colorado and Children's Hospital Colorado, Aurora.

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Advanced HIV as a Neglected Disease

Nathan Ford, D.Sc., Peter Ehrenkranz, M.D., and Joseph Jarvis, M.B., B.S.

In the early decades of the global response to HIV/AIDS, the focus was on saving lives. And rightly so: without antiretroviral treatment (ART), people lived less than a year, on average, from the time they developed AIDS. But over the past 15 years, the focus has shifted to virologic control. Since modeling and trials have shown that treating HIV could not only benefit the infected person but also eliminate transmission, viral suppression has become the main measure of success for HIV programs. Global targets have focused attention on the numbers of people who are tested, who begin receiving treatment, and in whom viral suppression is achieved. Reducing mortality is no longer a central metric.

For many years, HIV treatment was given only to people with a low CD4 count, who were at the highest risk for severe illness and death. In 2015, two large randomized trials showed that treatment should be started as soon as possible after infection. These results led to a rapid global shift in policy and funding, with the goal of getting as many people on treatment as early as possible. This change led to the perception that CD4 testing was no longer essential. To help pay for increased treatment coverage and assessment of its impact on virologic outcomes, donors and countries reduced their support for CD4 testing, and testing rates within ART programs declined rapidly. This shift occurred despite consistent inclusion of CD4 testing in clinical guidelines from the World Health Organization (WHO) and other leading authorities, who deemed it essential at baseline and when a patient returned to care.

Although treatment coverage

has increased substantially in recent years, any associated reductions in AIDS-related deaths have been smaller and slower than expected. The proportion of people with advanced HIV disease (defined by a CD4 count of less than 200 cells per cubic millimeter) remains high: it is estimated that more than 4 million people have advanced HIV disease, and each year more than 600,000 of them are expected to die.[1] Many of these deaths can be prevented — if the global HIV/AIDS community reconsiders who is at risk for the worst outcomes; determines what infections lead to the greatest morbidity and mortality; invests in new tools for diagnosing, preventing, and treating these conditions; and supports the systems required for delivering those tools effectively.

Until recently, advanced HIV was viewed as a problem of late presentation, so the solution was thought to be testing more people and diagnosing the disease earlier. Although late presentation remains problematic, however, advanced HIV is now predominantly seen among people who started care but were not effectively engaged or have disengaged, returning only when they're ill. Loss to care has long been recognized as a challenge, but we've only recently begun to recognize the extent to which cycling in and out of care increases the burden of advanced HIV disease.[2] The health risk posed by interrupting treatment is established: trial data show a precipitous drop in CD4 cell count within the first 2 months after treatment is stopped.[3]

The leading causes of HIV-related deaths appear to have changed little over time: they include tuberculosis, cryptococcal meningitis, and pneumocystis pneumonia, among others. But there have been few recent attempts to confirm empirically whether these infections are still the major killers of people with HIV in the highest-burden countries. Hospitalized HIV patients continue to routinely test positive for tuberculosis and cryptococcal meningitis, but these findings partly reflect availability bias: the diagnostics for these diseases are the ones most frequently available to clinicians. To address this gap, Emory University plans to launch a study in 2024 combining minimally invasive tissue sampling with rigorous cause-of-death analysis. The study will take place at hospitals in four African countries with varying geography, resources, and progress in epidemic response.

Meanwhile, all opportunistic infections remain challenging to manage with existing tools, and there are few new developments on the horizon. Recently, the WHO surveyed the research pipeline for advanced HIV and found very little research and development.[4] Overall, HIV is not a neglected disease — tens of billions of dollars have been invested in scaling up access to prevention and treatment. In the past decade, however, *advanced* HIV has become neglected, with limited attention paid to either consistently using existing tools or finding new tools for preventing AIDS-related deaths. As defined by the WHO, the "neglected tropical diseases" comprise 20 diseases and disease groups that cause devastating health, social, and economic consequences among the world's poorest people; they are defined by a lack of sufficient resources for and inadequate research attention to prevention, screening, diagnosis, and treatment. The same shortcomings now apply to advanced HIV disease.

Driving the neglect of advanced HIV is a shrinking ability to diagnose the problem. Key manufacturers of CD4 cell count tests are withdrawing from the market in low- and middle-income countries, judging that decreased demand means these tests are no longer needed. Conventional laboratory-based CD4 testing capacity is being defunded and dismantled, leaving treatment programs reliant on a very small number of rapid CD4 testing devices of variable performance, with no guarantees of sustainable access.

Once HIV disease becomes advanced, there are few tools for preventing and treating the resulting opportunistic infections. A survey conducted in 48 African countries up to the end of 2022 found limited capacity for diagnosing common opportunistic infections — in particular, pneumocystic pneumonia, cryptococcal diseases, and histoplasmosis.[5] There has been recent progress in some areas, including simpler, safer treatment for cryptococcal meningitis and promising new diagnostic tools for histoplasmosis and talaromycosis. The Drugs for Neglected Diseases Initiative is investing in new tools for managing cryptococcal meningitis; this investment is very welcome but also underscores the point that advanced HIV is being neglected by the pharmaceutical industry.

Meanwhile, for other opportunistic infections, progress remains minimal. These opportunistic infections include severe bacterial

infections, pneumocystis pneumonia, and toxoplasmosis — all among the leading causes of deaths since the HIV pandemic began, but all difficult to diagnose and treat in resource-limited settings where the burden is greatest. In November 2023, the Bill and Melinda Gates Foundation granted the University of Cape Town funding to conduct a large trial to assess whether providing azithromycin to all people with severe immunosuppression can reduce mortality from severe bacterial infections. This research is necessary but insufficient: results are not expected for 4 to 5 years, and with current funding the trial can include only adults. A key priority remains development and deployment of tools for preventing, diagnosing, and treating severe bacterial infections as part of a public health response attentive to risks of antibiotic resistance. Many other causes of AIDS-related death, including cytomegalovirus infection and cancers such as Kaposi's sarcoma, are extremely challenging to manage, and little research into new diagnostics and treatments is under way.

Once HIV disease becomes advanced, there are few tools for preventing and treating the resulting opportunistic infections.

Measurement drives and directs action. As global targets have focused attention on viral suppression, attention to mortality has diminished. National programs generally do not collate or report data on causes of HIV-related deaths; we therefore lack reliable estimates of mortality and the true scale of deaths related to advanced HIV disease. Although these data are complex to capture, reliable measurement of AIDS-related deaths, disaggregated by major causes, needs to be at the heart of surveillance at the national, regional, and international levels. A better understanding of the primary causes of death may motivate funders and policymakers to strengthen systems for delivering the services required for preventing deaths associated with advanced HIV disease.

Neglect of advanced HIV disease is an unintended consequence of the global shift in objectives from treating the sickest people to treating all who are infected. Improved access to antiretroviral therapy is necessary for reducing deaths, but it is not sufficient. We believe donors should continue supporting CD4 testing for diagnosing advanced HIV and guiding diagnosis and treatment of opportunistic infections. For patients with advanced HIV, medicine urgently needs better tools focused on the diseases that are confirmed to be the most prevalent in the relevant setting, so that we can respond effectively to the main causes of illness and death.

Disclosure forms provided by the authors are available at NEJM.org.

From the Department of Global HIV, Hepatitis, and Sexually Transmitted Infections Programmes, World Health Organization, Geneva (N.F.); the Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa (N.F.); TB and HIV Team, Division of Global Health, the Bill and Melinda Gates Foundation, Seattle (P.E.); and the Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, and the Botswana–Harvard AIDS Institute Partnership, Gaborone (J.J.).

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