More Evidence COVID Vaccines Work Well for People With HIV

People with suppressed HIV respond well to mRNA vaccines, but individuals with a low CD4 count may not be adequately protected.

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People living with HIV generally respond well to COVID-19 vaccines—especially if they receive booster shots—thereby dramatically reducing their risk of severe illness and death, according to several recent studies. But those with poorly controlled HIV or advanced immune suppression may not fare as well, underlining the importance of antiretroviral treatment.

As previously reported, early studies of COVID vaccine response among HIV-positive people found that those with well-controlled HIV and an adequate CD4 count could achieve SARS-CoV-2 antibody levels and T-cell responses comparable to those of HIV-negative people, though they might need additional doses to achieve full protection.

Now, with another year's worth of data, people with HIV can generally feel confident that COVID vaccines, as well as prior SARS-CoV-2 infection, provide good protection. But those with unsuppressed HIV or a low CD4 count—along with older individuals and those with underlying health conditions—may have slower, weaker or less durable immune responses and could potentially benefit from additional precautions.

COVID Outcomes

Raynell Lang, MD, of the University of Calgary, and colleagues with the Corona-Infectious-Virus Epidemiology Team looked at the risk of severe illness among people with and without HIV throughout the United States who had a breakthrough SARS-CoV-2 infection after vaccination.

As described in JAMA Network Open, the analysis included 1,214 HIV-positive and 2,408 HIV-negative adults who experienced breakthrough COVID through the end of 2021. About 90% were men and 60% were ages 55 or older. Most were on antiretroviral therapy with an undetectable viral load, and the median CD4 count was 620, but about a quarter had a prior history of AIDS.

All participants were fully vaccinated between December 2020 and June 2021 as defined at the time, meaning two doses of the Pfizer-BioNTech or Moderna messenger RNA (mRNA) vaccines or a single dose of the Johnson & Johnson vaccine. A small proportion (15%) had received a third dose.

Overall, both HIV-positive and HIV-negative people had low and comparable rates of severe illness, defined as hospitalization within 28 days after breakthrough COVID, at 7.3% and 6.7%, respectively. Regardless of HIV status, severe illness was more likely among people who received the J&J vaccine (9.3%), followed by the Pfizer-BioNTech (7.2%) and Moderna (6.2%) vaccines. Those who received a third dose were less likely to have severe illness.

Of the 249 hospitalized patients, 9.6% required mechanical ventilation and 8.0% died, with no differences according to HIV status. There was also no significant difference in the likelihood of death after a breakthrough infection whether hospitalized or not (1.0% for HIV-positive people and 0.8% for HIV-negative people).

However, the risk of severe breakthrough illness was 59% higher among HIV-positive people with a CD4 count below 350 compared with HIV-negative people. In a multivariate analysis among people with HIV, women, older people, those with a lower CD4 count and those with a cancer diagnosis had a higher risk of severe breakthrough illness. In particular, HIV-positive people with a CD4 count below 200 had more than a twofold increased risk of severe illness compared to those with a count of 500 or higher. Conversely, people who'd had a previous case of COVID-19—and presumably gained some natural immunity—had a lower risk.

Although vaccination effectively reduces the risk of severe COVID-19 illness for people with and without HIV, HIV-positive people with moderate or severe immune suppression "had a higher risk of severe breakthrough infection" and "should be included in groups prioritized for additional vaccine doses and risk-reduction strategies," the study authors concluded.

The Centers for Disease Control and Prevention now advises that the primary vaccine series for moderately or severely immunocompromised people—including those living with HIV—should consist of three doses of the mRNA vaccines, to be followed by recommended booster shots. As of last fall, this includes bivalent boosters better matched to the circulating coronavirus variants.

In another study, published in the journal AIDS, Line Rasmussen, MD, PhD, of Odense University Hospital, and colleagues looked at the risk of severe COVID among 5,276 adults living with HIV and 42,308 people in the general population of Denmark through the spring of 2022. About 70% were men, and the median age was 51 years. Most HIV-positive people were on antiretroviral treatment, and only 4% had a CD4 count below 200, but 45% had a prior history of advanced immune suppression. Nearly 90% of people in both groups had received two vaccine doses, and most had gotten a third dose.

Overall, the researchers saw "no major difference" between HIV-positive and HIV-negative people in the likelihood of testing positive for SARS-CoV-2. People with HIV were about twice as likely to be hospitalized with severe COVID, though the risk of death was statistically similar. People with HIV who received a third vaccine dose were less likely to test positive for SARS-CoV-2 and less likely to be hospitalized than those who got only two doses, and those ages 60 or older who received a third dose were less likely to die.

Immune Responses

Along with clinical outcomes, laboratory studies of immune responses—including antibody levels, whether antibodies are capable of neutralizing SARS-CoV-2, the ability of memory B cells to produce antibodies and T-cell responses—can shed light on how well COVID vaccines protect people living with HIV.

As described in the Journal of Infectious Diseases, Zabrina Brumme, PhD, of the British Centre for Excellence in HIV/AIDS in Vancouver, and colleagues analyzed antibody responses after three vaccine doses in 99 HIV-positive people on suppressive antiretroviral treatment and 152 HIV-negative people. (This is a follow-up to a previous report of outcomes after two doses.)

Among the HIV-positive participants, most of whom were men, the current median CD4 count was about 700, but the nadir, or lowest-ever, level was about 280, and about a quarter had fallen to just above 100. Most participants initially received the Pfizer-BioNTech or Moderna mRNA vaccines, but a small number got the AstraZeneca-Oxford vaccine (which was never authorized in the United States). Most people with HIV received a Moderna booster.

Antibody responses were measured up to six months after the second vaccine dose and up to one month after the booster dose. According to this report, published in June 2022, antibody levels and neutralizing activity naturally declined after the initial two-dose vaccine series, but they did not fall faster or reach a lower level in HIV-positive compared with HIV-negative people. However, a later report published this month, looking at a larger Canadian cohort, showed that while similar proportions of HIV-positive and HIV-negative people had adequate antibody levels three months after the second dose, a slightly lower proportion of people with HIV still had vaccine-induced immunity six months after the second dose.

After a third dose, responses in people with HIV were comparable to or even higher than those of HIV-negative people. In both groups, antibodies were substantially higher after the third dose compared with the second dose, but their ability to neutralize SARS-CoV-2 omicron variants was diminished relative to the original wild-type, or Wuhan, strain. There was no evidence that people with a low nadir CD4 count had poorer responses.

Another analysis by the same team, described in AIDS, looked at the durability of antibody responses after three vaccine doses in 64 people with HIV on suppressive antiretroviral therapy and 117 HIV-negative people. The researchers measured responses against wild-type and omicron BA.1 and BA.5 variants at one, three and six months after the third dose.

All antibody measures increased after the third dose compared with the second dose, but BA.1-specific responses—and even more so BA.5-specific responses—remained significantly lower than responses to the wild-type strain. Antibody concentrations in the blood declined at comparable rates after the third dose in people with and without HIV who had not had COVID, and antibody function also declined similarly in both groups. Six months after the third dose, more than 80% of HIV-positive people and more than 90% of HIV-negative people no longer had detectable BA.1 neutralization. However, having a breakthrough SARS-CoV-2 infection boosted antibody numbers

and function above vaccine-induced levels in both groups.

Based on these findings, the researchers recommended that, due to declining antibody levels over time, both HIV-positive and HIV-negative people who did not get COVID—and thus did not develop so-called hybrid immunity—could benefit from a fourth vaccine dose within six months after the third shot.

Current antibody levels don't tell the whole story, however. Antibodies normally decline after infection or vaccination, but memory B cells and T cells are left behind to respond if the threat is encountered again. This so-called cellular immunity does not reliably prevent infection, but it reduces the risk of severe disease. However, B-cell and T-cell responses are harder to measure than antibody levels.

As described in AIDS, Oriol Bestard, MD, PhD, of the Autonomous University of Barcelona, and colleagues assessed memory B-cell and T-cell responses among 11 HIV-positive and 39 HIV-negative people after recovery from mild or severe COVID.

Six months after SARS-CoV-2 infection, most people with and without HIV still had antibody-producing memory B cells. Almost everyone with severe COVID, regardless of HIV status, still had active SARS-CoV-2-specific T cells, falling to about two thirds of those who had mild illness.

Another study of Black people in South Africa who received the AstraZeneca-Oxford vaccine, reported in AIDS, found that HIV-positive and HIV-negative individuals had similar T-cell responses. Here, too, hybrid immunity after both vaccination and SARS-CoV-2 infection resulted in heightened T-cell responses.

People at Higher Risk

Older people tend to have weaker immune responses after infection or vaccination. As reported at the Glasgow HIV Drug Therapy meeting in October, researchers in Amsterdam compared immune responses in 195 people with well-controlled HIV and a high CD4 count and 246 HIV-negative people ages 55 and older. Reassuringly, people with and without HIV had similar antibody responses three months after COVID vaccination, regardless of whether they also had a SARS-CoV-2 infection—and cellular immune responses were actually higher in the HIV-positive group.

But outcomes are not so reassuring for HIV-positive people with a low CD4 count.

As described in the Journal of Infectious Diseases, Beatriz Mothe, MD, PhD, of Hospital Universitari Germans Trias I Pujol near Barcelona, and colleagues looked at antibody and cellular immune responses after mRNA vaccination in 58 HIV-positive people with a CD4 count below 200, 36 HIV-positive people with a CD4 count above 500 and 33 HIV-negative people.

Four weeks after the second vaccine dose, antibody levels were substantially lower in people with a CD4 count below 200 than in HIV-positive people with an adequate CD4 count, who in turn had slightly lower levels than HIV-negative people. What's more, antibody neutralization capacity and

SARS-CoV-2–specific T-cell responses were absent or reduced in one third of people with a low CD4 count compared with just 4% of those with a count above 500.

Similarly, Marta Sisteré-Oró, PhD, of Universitat Pompeu Fabra in Barcelona, and colleagues analyzed antibody and cellular immune responses in a small group of immunological nonresponders, that is, people with HIV who do not experience full CD4 cell recovery despite antiretroviral treatment. They compared responses to the Pfizer-BioNTech vaccine in 10 HIV-negative people and 10 HIV-positive people who had been taking antiretrovirals for at least six months. Although 80% had an undetectable viral load, eight still had a CD4 count below 200, and two had a count between 200 and 350.

As reported in Frontiers in Immunology, compared with the HIV-negative participants, all of whom responded well, half of the HIV-positive people showed inadequate immune responses after two vaccine doses. Three of the five nonresponders who received a booster then mounted a response, but two remained poorly protected.

Finally, in a letter to the editor in the Journal of Clinical Virology, Nolan Hassold, of Hôpital Avicenne in France, and colleagues described inconsistent outcomes following a booster in previously nonresponsive people with HIV. The researchers previously reported on HIV-positive people who did not achieve adequate SARS-CoV-2 antibody levels after two Pfizer-BioNTech or Moderna vaccine doses. Between December 2021 and April 2022, 23 individuals who had not yet gotten COVID received a booster dose six months after their primary vaccination. CD4 counts improved between the first and third dose after they started antiretroviral therapy. Antibodies generally rose, but six people still did not reach protective antibody levels even after the third shot, despite five of them having an increased CD4 count. Five people who contracted COVID after receiving a booster had mild or no symptoms, but two persistent nonresponders with very low antibody levels—one of whom had only 15 CD4 cells—died despite intensive care.

The Bottom Line

Taken together, these studies provide reassurance that most people with HIV respond well to COVID vaccines, including those with a previous history of a low nadir CD4 count. But those with a persistent immune suppression remain at risk for severe illness.

Inadequate vaccine response among people with poorly controlled HIV or a low CD4 count is a concern, given that around one third of people living with HIV in the United States are not in care. For those who are not on treatment, starting antiretroviral therapy is a key step toward protection against COVID-19 and better overall health.

Those with a detectable viral load or a persistently low CD4 count despite taking antiretrovirals should talk with their doctor about optimizing their regimen. For those who still don't have adequate CD4 recovery, pre-exposure prophylaxis using monoclonal antibodies may be an option, but unfortunately, Evusheld—the only authorized therapy for COVID PrEP—may not be effective against the latest omicron variants.

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