Immune Responses to SARS-CoV-2 Vaccination in People With HIV: A Tale of Two Pandemics

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Suppressive antiretroviral therapy (ART) preserves and, indeed, restores CD4 T lymphocyte counts and immune function in individuals with HIV infection. People with HIV (PWH) receiving effective treatment are no longer susceptible to severe and opportunistic infections and neoplasms that characterize the acquired immune deficiency syndrome

(AIDS). Nonetheless, less severe immune dysfunction, lower level inflammation and immune cell senescence persist [1]. The degree of ongoing inflammation correlates with slower and less complete CD4 T cell recovery [2]; comorbidities such as cardiovascular disease, neurocognitive decline, and frailty [3]; and poorer immune responses to vaccines [4].

Uncontrolled viremia strongly impairs immune responses to vaccines in PWH, and the induced pathogen-specific neutralizing antibodies wane more quickly [5-7]. The viral suppression from initiating ART substantially, but incompletely, improves the magnitude and durability of these responses [8,9]. This ART-induced viral suppression seems to be the most important factor in improving immune responses to vaccines [8,9], but CD4 T cell count is also associated with vaccine responses. Stronger responses are seen in PWH with CD4 cell counts >200 cells/mm^3 [5-7] There is also evidence that the legacy of immune damage prior to initiating ART is important in determining current vaccine effectiveness, as the nadir CD4 T cell count has correlated with antibody responses to vaccines in some studies [5-7]. To address this problem, more and higher doses of vaccine, as well as the use of more potent adjuvants, have been utilized to enhance vaccine immunogenicity in PWH [5-7].

In this issue of *The Journal of Infectious Diseases*, Lapointe, et al. compared the humoral immune responses generated against wild-type and Omicron strains before SARS-CoV-2 vaccination; at one month, 3 months, and 6 months after the second dose of a two-dose vaccination; and then one month following the third "booster" dose in 99 PWH receiving suppressive ART with 152 HIV negative controls [10]. They measured anti-spike protein

receptor-binding domain (RBD) antibodies, ACE2 displacement, and live virus neutralization. Most study participants received an initial two-dose mRNA vaccine regimen (83% PWH, 99% controls); the others received either a two-dose ChAdOx1 regime (8%PWH, 1% controls) or a heterologous mRNA-ChAdOx1 regimen (8% PWH, 2% controls). The booster immunization was with an mRNA vaccine. The median recent CD4 T cell count was 715 cells/mm^3; the median nadir CD4 T cell count was 280 cells/mm^3. Notably, the analyses adjusted for sociodemographic, health, and vaccine-related factors.

PWH did not have lower antibody concentrations or viral neutralization activity at any time point measured, nor did they manifest a faster rate of antibody decline after two vaccine doses. The most recent or nadir CD4 T cell counts did not affect antibody concentrations, either 6 months after the second vaccine dose or 1 month after the third dose, nor the rate of antibody decline after the second dose. Antibody levels and neutralization titers were boosted substantially in both cohorts after the third dose, but these activities were consistently lower against Omicron than against wild type SARS-CoV-2. The titers in PWH were actually higher than in the HIV-negative controls after boosting with the third dose, but the majority of the PWH who received the mRNA-1273 vaccine at this time may have received the higher (original) dose, as recommended.

Overall, the study was very well organized and conducted, with the “real world” analyses accounting for important confounding variables. The multivariable analyses of the study contribute to its strength but, of course, these analyses are dependent on the assumptions made. For example, equal weight to potentially influence immune responses to the vaccines was given to each of the comorbid conditions considered. But some conditions such as

immunosuppression will have more of an influence on vaccine immunogenicity than others such as hypertension. Furthermore, other known and unknown confounders can affect results in real-world studies. The ongoing, shifting landscape of the SARS-CoV-2 pandemic, and the government and community responses to it, affect the conduct of study protocols. For example, as a result of government prioritization decisions, the vaccination schedule differed between the PWH and HIV negative groups with regard to the waves of variant strain infections. The post-third vaccine dose study visit occurred just after the first Omicron wave for the majority of the PWH group, while most of the control group, the majority of whom were health care workers, had their third doses and post-third dose vaccination visit earlier. The authors believe this, and not increased susceptibility to infection, accounts for the higher rate of overall post-vaccination infections in the PWH group than in the control group (18% vs. 9%). On the other hand, because of the greater exposure to Omicron, it is also conceivable that the PWH group had a higher rate of unrecognized asymptomatic or mild Omicron infections that may have contributed toward boosting the immune responses measured at the post-third dose visit.

To be sure, these factors are unlikely to affect the results enough to detract from the general conclusion that the magnitude and durability of humoral immune responses to mRNA vaccination in ART-treated PWH with high CD4 T cell counts are similar to those in HIV negatives. The “real world” finding that HIV-infected individuals receiving effective ART have essentially equivalent antibody responses to SARS-CoV-2 vaccination is important for the field. Since PWH may be more susceptible to more severe illness from SARS-CoV-2 infection [11,12], there is a need to determine the optimal vaccine strategy for them.

The study confirms the findings of most other investigations of PWH who received either the CHAdOx1 vaccine or an mRNA vaccine; namely that SARS-CoV-2 vaccination induced humoral and cellular immune responses comparable to HIV negative individuals in ART-treated PWH with high CD4 T cell counts [13-17]. In one study of 143 ART-treated PWH with high CD4 T cell counts and 261 health care worker controls who received the BNT 162b2 mRNA vaccine, while the rates of anti-RBD-seroconversion (97% vs 99%) and anti-pseudovirus neutralization positivity (97% in PWH) were similar, the geometric mean anti-RBD and neutralization titers were moderately lower in the PWH group [18]. The Lapointe et al. study provides important additional data regarding the durability of these responses and the effective boosting of these responses against the wild type and recent Omicron SARS-coV-2 strains after an additional dose of mRNA vaccine. Taken together, all these data are reassuring for ART-treated PWH with high CD4 T cell counts.

Evidence is accumulating that antibody titers, and in particular neutralization titers, correlate with protection from infection and disease [19]. Nevertheless, other antibody functions and cell mediated immunity, as well as mucosal host defenses may also contribute. Studies to-date suggest that cellular immune responses to SARS-Cov-2 vaccination are not compromised in ART-treated PWHs with high CD4 T cell counts [13-15]. Nevertheless, further investigation of the effect of SARS-CoV-2 immunization on actual infection risk in PWH is urgently needed. The durability of immune responses and protection from infection and illness beyond 6 months should be assessed.

Other subpopulations of PWH are likely to respond very differently to SARS-CoV-2 immunization. If the experience with other vaccines is informative, viremic individuals will

not achieve the same protection from SARS-CoV-2 vaccination. Several studies have found that PWH with CD4 T cell counts <200 cells/mm^3 mount inferior humoral immune responses to SARS-CoV-2 immunization compared to immunocompetent people without HIV infection [20-23]. Notably, there is sparse published information about SARS-CoV-2 vaccine-induced responses in children with HIV. These groups of PWH need to be systematically investigated to determine optimal vaccination strategies.

In sum, this study provides further testament to the potency of ART in restoring immune function in PWH, allowing them to benefit from the protective effects of SARS-CoV-2 immunization. As such, it gives further voice to the need to identify and treat all those with known and unrecognized HIV infection, and to immunize them against SARS-CoV-2. This is a tale of two pandemics – of how treating HIV infection can help control the SARS-CoV-2 pandemic.

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