SARS-CoV-2 Vaccination in the Context of Ongoing HIV Cure-Related Research Studies

To the Editors:

The SARS-CoV-2 pandemic has affected research efforts worldwide. Previously, we described our strategy to mitigate COVID-19 transmission risk during an ongoing HIV cure-related clinical trial. SARS-CoV-2 vaccines recently have been authorized for emergency use and will become available to people with HIV imminently. As a result, researchers must determine how to adjust study protocols to incorporate the likelihood that participants may be vaccinated.

In many cases, SARS-CoV-2 vaccination is unlikely to interact with study interventions or outcomes, either because of the nature (eg, not involving mechanisms that would be expected to be altered by immune activation or inflammation) or timing (eg, a single therapy administered regularly for a duration of months or years) of the investigational interventions or measurements. In such cases, it is possible that the effects caused by a highly immunogenic vaccine are likely to be transient and unlikely to interfere with study interventions or outcomes over the long term. Furthermore, some studies can be postponed. However, ongoing HIV cure-related studies involving immunotherapy or analytic treatment interruption (ATI) face substantial challenges. First, study interventions, particularly immunotherapy or ATI, might affect the safety and/or efficacy of the SARS-CoV-2 vaccine. Second, the immunologic effects of vaccination might confound the study’s scientific findings. Third, previous counseling and informed consent is not likely to have included detailed discussion around SARS-CoV-2 vaccination.

To address these challenges (Table 1), our biomedical study team, social scientists, and community advisory board met to determine the optimal approach to SARS-CoV-2 vaccination within an ongoing study in which immunotherapies are followed by an ATI (NCT04357821), then broadened our considerations to our larger immunotherapy program.

Our team believed that it was unacceptable to discourage or even delay SARS-CoV-2 vaccination during the study period. We recognized that participants could be offered vaccination from diverse sources contingent on local guidelines, making it unlikely that all participants would be offered vaccination simultaneously or at a predictable time.

Our goals were as follows: (1) to avoid delays in accessing SARS-CoV-2 vaccination, once it is available, (2) to minimize the effects of study interventions on vaccine safety and efficacy, and (3) to minimize the effects of SARS-CoV-2 vaccination on study results. Before the COVID-19 pandemic, the study protocol outlined that a participant should not receive any vaccination within 7 days of enrollment or be exposed to any experimental vaccination within 90 days of enrollment. Participants were supported by funding from the National Institute for Allergy and Infectious Disease at the National Institutes of Health to MJP (T32 AI60530-12), the amfAR Institute for HIV Cure Research (amfAR 109301), the Delaney AIDS Research Enterprise (DARE) (UM1AI126611), and the National Institute of Mental Health to K.D. (R21MH118120). M.J.P. receives support from the UCSF Resource Allocation Program. S.G.D. reports grants and/or personal fees from Gilead Sciences, Merck & Co, and Viiv, consulting fees from AbbVie, and serves on the Scientific Advisory Board of Enochian BioSciences. The remaining authors have no funding or conflicts of interest to disclose. The authors are pleased to make available the materials referred to in this article on request. Please contact michael.peluso@ucsf.edu to request the most recent version of these materials.

TABLE 1. Key Considerations Related to SARS-CoV-2 Vaccination

| Participant considerations | Effect of the study on vaccine safety and/or efficacy | Effect of the vaccine on the study |
|-----------------------------|------------------------------------------------------|-----------------------------------|
| When is SARS-CoV-2 vaccination expected to be available to each study participant? | Can enrollment into the study be delayed? | Are there study results that could be affected by SARS-CoV-2 vaccination? |
| Where will each participant receive their SARS-CoV-2 vaccination? | Which study interventions might affect the safety and/or efficacy of the SARS-CoV-2 vaccine? | Will delaying study product administration lead to logistical challenges regarding product availability or viability? |
| Which SARS-CoV-2 vaccine will be made available to each study participant? | How can the study schedule be adjusted to accommodate SARS-CoV-2 vaccination? | How should SARS-CoV-2 vaccination be accounted for in the analysis phase? |
| How should a participant be counseled regarding the risks and benefits of SARS-CoV-2 vaccination during the study? | How should the study approach a situation in which a participant has already begun a phase of the study that could affect vaccine response? | Other considerations |
| Effect of the study on vaccine safety and/or efficacy | Can the study navigate participants to COVID-19 vaccination? | Should study participants be required to be vaccinated for SARS-CoV-2? |
| Effect of the vaccine on the study | Should participants be asked to provide documentation of SARS-CoV-2 immunization before enrolling on continuing in the study? | Should participants be vaccinated? |
| Are there study results that could be affected by SARS-CoV-2 vaccination? | Should additional considerations be made based on the details of the SARS-CoV-2 vaccine, ie, made available to the participant (eg, manufacturer, single dose versus two-dose series, and adenovirus vector versus lipid nanoparticle)? | How should a situation in which a participant declines to report SARS-CoV-2 vaccination plans or status be addressed? |
| Will delaying study product administration lead to logistical challenges regarding product availability or viability? | How should SARS-CoV-2 vaccination be accounted for in the analysis phase? | What approach should be taken if the second vaccine in a 2-vaccine series is delayed? |
| How should SARS-CoV-2 vaccination be accounted for in the analysis phase? | Other considerations | What approach should be taken if a participant chooses not to be vaccinated and later changes his or her mind? |
encouraged to receive routine vaccinations before enrollment, but clinically required vaccinations are allowed during the study period as long as they are spaced 1 week from study interventions or measurements. Most participants are able to carefully plan for routine vaccinations based on the anticipated study schedule. However, the need for participants to urgently receive a highly immunogenic vaccine, in most cases requiring 2 doses with unpredictable availability, to protect against a newly identified pathogen associated with substantial morbidity and mortality was not anticipated when the study was initially implemented.

The study consists of 5 phases of interventions, including immunotherapy and ATI, and takes place over up to 2 years. To address the issues related to SARS-CoV-2 vaccination, our team reviewed the protocol and identified key time points where interventions would be expected to affect vaccine efficacy. This included periods of immunotherapy and the ATI, during which vaccine responses could be suboptimal due to iatrogenic immune suppression. We then identified the study’s key biological endpoints, using these determinations to identify optimal time points for SARS-CoV-2 vaccination, and developing plans to pause the study at these points if it was likely vaccination would be offered to the participant imminently. Realizing that we cannot plan for all contingencies, we anticipate protocol deviations and violations will occur, which our IRB agreed was to be expected.

Through this process, we hope to be able to continue the study while maximizing participants’ safety and minimizing the impact on trial results.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contributions of the amfAR and DARE Community Advisory Boards. The authors thank Dr. Rowena Johnston from amfAR for her support.

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