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CHAPTER

COVID-19 vaccines for high risk and immunocompromised patients

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1 Introduction

The COVID-19 pandemic has had a major negative impact on public health and its worldwide infrastructure and resources. Perhaps the most recognized devastating outcomes of this crisis are the high rates of morbidity and mortality, and the toll it has taken on people who have underlying co-morbidities or risk factors (Garg et al., 2020). Among these, include groups within the general population who are diabetic (Garg et al., 2020; Gao et al., 2020), obese (de Frel et al., 2020), elderly (Centers for Disease Control and Prevention, 2021), and possibly immunocompromised (Kates et al., 2020; Office of the AIDS Research Advisory Council, 2021), especially people who are infected with the human immunodeficiency virus (HIV) and who subsequently progress to developing acquired immunodeficiency disease (AIDS) (Office of the AIDS Research Advisory Council, 2021). Many of these well-characterized victims have a more severe course of COVID-19, leading to increased numbers of hospitalized patients and deaths relative to the percentages occurring in people having little or no pre-conditions (Garg et al., 2020), although, as will be discussed later on, the pattern in the HIV/AIDS group has been reported to be less clear and inconsistent (Office of the AIDS Research Advisory Council, 2021). Also included in this latter group having immune defects are transplant recipients, cancer patients and autoimmune cases where an immunocompromised or hyperimmune condition leads to intense treatment with certain medications that adversely affect various components of the immune system. The key reasons why
high-risk factors lead to increased susceptibility to COVID-19 are summarized in Table 1, and are similar to the role they play in the pathogenesis of various other infections. Fortunately, several different types of vaccines are now available that can be used to protect these susceptible patients from developing serious, life-threatening disease due to the etiologic agent of COVID-19, SARS-CoV-2. In this regard, this chapter focuses on some of the subtle nuances and challenges that COVID-19 vaccines play in protecting people who are at the greatest risk for developing serious illness using HIV/AIDS as the primary example.

### Table 1 Immune defect-related conditions/host factors potentially putting people at greater risk for a negative outcome due to COVID-19 and their status as potential vaccinees.

| Defect or host condition | Cause or mechanisms                                                                 | Candidate for a COVID-19 vaccine |
|--------------------------|------------------------------------------------------------------------------------|---------------------------------|
| HIV infection/AIDS       | HIV-mediated gradual killing of CD4⁺ T cells                                       | Yes a                           |
| Type 2 diabetes          | Hyperglycaemia interferes with killing by phagocytic cells                          | Yes                             |
| Obesity                  | Adaptive immune system dysfunction; slight lymphopenia and poor regulation of ACE2 receptor | Yes                             |
| Aging                    | Immunologic “memory” tends to decline with age                                     | Yes                             |
| Cancer                   | Chemotherapy or immune checkpoint inhibitors interfere with various immune functions | Yes b                          |
| Organ transplant         | Immunosuppressive drugs used to prevent rejection of the transplant also interfere with various immune functions | Yes b                          |
| Autoimmune disorder      | Treating with anti-inflammatory agents and/or immune modulators interferes with various immune functions | Yes b                          |

*Humoral immunity may be weakened in some patients due to severely reduced numbers of potentially reactive T cells needed to assist B cells to differentiate into antibody-producing plasma cells; activation of cell-mediated immunity (in the form of cytotoxic T cells) directed against many pathogens is also severely depressed; vaccine recipients may require multiple boosters.

*Immune response impairment is somewhat similar to HIV-infected patients but the loss of activated T cells is less severe, possibly making the need for multiple boosters not as frequent or less likely.

2 Development of COVID-19 vaccines

The speed with which safe and effective vaccines have been developed to prevent COVID-19 has been nothing short of being extraordinary and perhaps even beyond original expectations. In just about a few months after the pandemic became recognized as an almost unparalleled global catastrophe and a sense of urgency had crept into the picture, potential vaccines were produced by several manufacturers and became available for testing. This outcome is a testament to the hard work and diligence of the research community and pharmaceutical industry in cooperating
in this venture, along with the huge response of the general population willing to participate in clinical trials that were needed to verify the worthiness of these vaccines. Even many of the recognized medical/scientific “experts” had predicted that vaccines would likely not be available for routine use for about 1.5–2 years after the initiation of experiments in trying to develop them. Certainly, in the back of many minds was the gloomy feeling that it may even take much longer given the relative lack of success, after much effort and a large amount of funds had already been invested, over a span of many years, in trying to develop highly effective vaccines for malaria, HIV infection and EBOLA virus disease (EVD)—diseases having high rates of morbidity and mortality (similar outcomes to COVID-19), but which have been known and well characterized for well over a century (for malaria) and for nearly a half century (for HIV infection and EVD). On the other hand, the annual development of vaccines to combat influenza (aka “the flu”) caused by the genetic variants of the influenza virus did offer encouragement that an effective COVID-19 vaccine could be produced within a relatively short period of time.

In the United States, as of November 2021, two types of anti-COVID-19 vaccines are in use and available to everyone from ages 5 and above. For several months prior to this, only people >11 years of age were eligible to receive any one of these vaccines based on authorizations made by the U. S. Food and Drug Administration (FDA) followed by recommendations from the Centers for Disease Control and Prevention (CDC). One type of vaccine consists of purified messenger RNA (mRNA) given in two intramuscular injections with the 2nd injection given 3–4 weeks after the first one. In October, 2021, an additional booster injection was recommended by the FDA and the CDC for those recipients who completed their initial series at least 6 months previously and who are > 65 years of age or have certain other risk factors. Soon after this announcement was made, the booster recommendation was amended to include everyone ages 18 and older. The mRNA encodes for the SARS-CoV-2 spike protein. The other vaccine has a viral vector formulation with a live but safe adenovirus serving as the vector for carrying the genome of the SARS-CoV-2 spike protein and, until recently, it was thought that a second booster injection would not be needed for one of the two viral vector versions currently available. However, serious consideration is now being given to modify this strategy to include additional boosters for all vaccines with allowances for “mixing and matching” with the mRNA vaccines based on recommendations by the FDA to be followed by further consideration by the CDC. In both cases, the spike protein had been shown to be highly immunogenic and the key protective component in pre-clinical studies, and is associated with a vigorous antibody response. The time frame for these events was as follows. After an initial Emergency Use Authorization (EUA), that was issued in December 2020 and then followed by a second one in February 2021 by the FDA, the two mRNA vaccines produced by Pfizer (Pearl River, NY) and Moderna (Cambridge, MA) have either received final approval or are pending final approval for routine use as of late October 2021. This is also true for the viral vector vaccines produced by Janssen/Johnson & Johnson (Titusville, NJ) and Astra-Zeneca (Cambridge, UK) which have received an EUA for adults (> 15 year’s old) in the U.S. It should be noted that in the United Kingdom much earlier approval was given
in December 2020 and January 2021, for some of these vaccines, by the U.K. Health Department, following recommendations by the Medicare and Health Care Regulatory Authority in the Department of Health and Social Care. It is worth noting that, from the very beginning, the rapid deployment of these vaccines, especially in the U.S., was partially aided by the involvement of the U.S. federal government under the program known as “Operation Warp Speed” (United States Federal Government, 2020). Although some people may have viewed this program as having political overtones, it nonetheless did provide considerable financial and logistical support to the pharmaceutical industry for accelerating the development and distribution of multiple vaccine doses throughout much of the U.S. in a nearly unprecedented and efficient fashion. Also, as an additional benefit of this process, starting in June 2021, surplus vaccine that was being produced in the U.S. (as well as by some of the other vaccine-producing countries) was then shipped abroad to various countries that were unable to procure enough vaccine to immunize their citizenry. Still, despite these humanitarian efforts, in some low-income countries, less than 1% of the population is fully vaccinated, and the success rate is only slightly better in lower-middle-income countries, compared with more than half in high-income countries. Thus, such a situation reinforces the ongoing problem of trying to achieve global vaccine equity. Another related challenge/concern, as pointed out in another chapter of this volume (Pavia, 2022), is that universal acceptance of the COVID-19 vaccines is lacking due mostly to hesitancy and the spread of misinformation or a general lack of a full understanding on the overall benefits of getting vaccinated amid a worldwide medical disaster. Unfortunately, these anti-vaccine sentiments still linger and will continue to be deeply engrained in the minds of an ignorant subpopulation and others unwilling to accept well established facts long after the pandemic has passed.

3 The use of COVID-19 vaccines for the high-risk patient population with the emphasis on HIV-infected patients

As with the general population, people who are diabetic, obese, elderly and immunocompromised, such as those with HIV/AIDS, should be strongly encouraged to receive one of the available vaccines as a preventive measure against developing COVID-19. Interestingly, there appears to be an intriguing association/connection between diabetes and obesity. In this regard, although not all obese individuals have type 2 diabetes mellitus, and not everyone with type 2 diabetes mellitus is obese, it is known that obesity is the most important environmental risk factor for diabetes and, in fact, more than 80% of patients with this condition are obese (Kumar, Abbas, & Aster, 2020). The major problem in type 2 diabetes mellitus is hyperglycaemia which causes dysfunction of the immune response so that these patients become more susceptible to infections (Berbudi, Rahmadika, Tjahjadi, & Ruslami, 2020). There have been many studies to determine what else is involved as to why this risk factor impairs the host immune defense, especially against pathogens. The mechanisms that have been elucidated include suppression of cytokine expression, defects in phagocytosis leading to the failure to kill microorganisms, and reduced activation
of lymphocytes in response to a stimulus (Berbudi et al., 2020). Therefore, both innate immune response defects, such as dysfunction of neutrophils and macrophages and of the adaptive immune response (including T cells) are thought to cause weaknesses of host defense mechanisms against invading pathogens (Berbudi et al., 2020). With regards to the role that obesity plays in this context, McLaughlin, Ackerman, Shen, and Engleman (2017) suggested that chronic inflammation in adipose tissue is likely to play an important role in the development of obesity-associated insulin resistance that is characteristic of type 2 diabetes. This inflammatory response may be related to adipose cell hypertrophy, hypoxia, and/or intestinal leakage of bacteria and their metabolic products, and that M1 macrophages, interferon-gamma secreting Th1 cells, CD8+ T cells and B cells promote insulin resistance partly through secretion of proinflammatory cytokines (McLaughlin et al. (2017)). Another study (Richard, Wadowski, Goruk, et al., 2017) having similar findings suggests that patients with obesity and type 2 diabetes mellitus have additional immune dysfunction when compared to obese individuals who are metabolically healthy. These immune abnormalities include impaired neutrophil function and T cell responses to antigenic challenge.

Foremost among these risk groups having immune-associated defects, it would seem that people with HIV/AIDS would benefit most from getting vaccinated given their severely immunocompromised condition in the absence of any anti-retroviral treatment designed to improve/restore their immune function. This is because HIV infection mainly targets the immune system, though many other tissue sites and organs can be affected. AIDS, which is caused by HIV, results in a severe immunodeficiency, mostly affecting cell-mediated immunity, via infection and death of CD4+ T cells and impairment in the function of surviving helper T cells after the virus enters the body via mucosal tissues and blood where it can also infect macrophages and dendritic cells (Murray, Rosenthal, & Pfaller, 2020). These latter two cell types play a key role as being antigen-presenting cells, along with B cells, that are involved in the somewhat complex yet coordinated process of eventually producing antibodies intended to neutralize the virus. Collectively, these events that are mediated by HIV severely disrupt a good portion of the human body’s defense mechanisms against infectious disease by preventing activation of primarily the adaptive immune response. In addition, HIV becomes established in lymphoid tissues of the body and may remain latent for a long period of time, which is variable. This leads to a major and continuous breakdown of host defenses, a large increase in the viral load, and profound, life-threatening clinical disease. The typical person with AIDS presents with long-lasting fever (>1 month), fatigue, weight loss, diarrhea, and generalized lymph node enlargement. After a period of time which varies, a wide range of serious opportunistic infections, secondary neoplasms, or clinical neurologic and renal disease may develop (Murray et al., 2020). Without treatment, most patients with HIV infection progress to AIDS after a chronic phase lasting from 7 to 10 years. However, over the past few years, highly active antiretroviral therapy (HAART) is a regimen that has been widely used to manage and treat HIV/AIDS patients with considerable success in many cases (Saag, 2021).

Surprisingly, in the overall picture, some evidence to date (reviewed in Brown, Spinelli, & Gandhi, 2021) does not suggest that HIV/AIDS patients have a markedly
higher susceptibility to SARS-CoV-2 infection, although disparities in the social determinants of maintaining good health and certain other comorbidities likely have a greater influence, especially with regards to gaining access to supportive health care and continuation of treatment regimens such as HAART. Inconsistencies exist, in this regard, since there are also other reports from separate facilities describing increased, decreased, or no difference in outcomes of COVID-19 in this patient population, especially in terms of the fatality rate (Bertagnolio et al., 2021; Boulle et al., 2020; Johnston, 2021; Office of the AIDS Research Advisory Council, 2021). These studies have come from various locations, each with a different underlying HIV prevalence and access to various treatment regimens. The majority of the published literature has not supported a significantly higher risk for severe disease among HIV/AIDS patients in the United States and Europe (Brown et al., 2021; Office of the AIDS Research Advisory Council, 2021), although a large, population-based study in South Africa reported a higher rate of death due to COVID-19 (Boulle et al., 2020). Higher rates of comorbidities associated with COVID-19 severity among HIV/AIDS patients is an area that still needs to be evaluated and monitored closely. The immediate impact of COVID-19 is that it could lead to decreased access to HIV prevention services and HIV testing, and hampering HIV treatment access and virologic suppression, which could lead to worsening of HIV control and delays in achieving other desirable positive outcomes. Also, along these lines, the CDC has concluded (CDC, 2020) that people with HIV who are on effective HIV treatment have the same risk for developing COVID-19 as people who do not have HIV, although the risk for people with HIV becoming seriously ill is greatest for those who have a low CD4 T-cell count and are not on effective HIV treatment such as with HAART.

In light of the foregoing, what are some of the relevant intervening factors that could influence the response pattern of the HIV/AIDS patient population to COVID-19? Examples of these variables are as follows:

(i) What is the stage (early versus late) of HIV infection?
(ii) What is the current plasma HIV load?
(iii) What is the current peripheral blood CD4+ count?
(iv) Is the patient currently receiving HAART?
(v) And, if so, for how long (just starting versus long term), and how is the patient responding to HAART?
(vi) Is the patient currently co-infected with an opportunistic pathogen?

With this information in mind, additional questions arise pertaining to the use of COVID-19 vaccines for the HIV/AIDS group, and they include:

(i) Are the vaccines safe and what level of protection would these vaccines offer to this patient population?
(ii) And if so, which vaccine should be administered to them?
(iii) How often should they receive booster injections?
(iv) And at what point, if at all, should they be vaccinated after they have recovered from a naturally acquired infection with SARS-CoV-2?
The answers to most of these questions are relatively straightforward and not too complicated. According to the CDC (2020), the U.S. vaccine safety system makes sure all vaccines are as safe as possible. COVID-19 vaccines have gone through rigorous safety tests and have met or even exceeded similar standards as for other vaccines that have been produced for nearly a century and have been in routine use for over 60 years. People with HIV have been included in clinical trials, though there is limited safety and efficacy data available as they pertain specifically to this group. So far, there are no data indicating that the vaccines are not safe and effective for people with HIV, including adolescents between 12 and 15 years nor has it been shown that the COVID-19 vaccines interfere with the effectiveness of HIV medications used in certain treatment regimens, such as HAART. There have been no unusual links or enhanced negative reactions between HIV or other types of immunosuppression with any of the rare serious adverse events that have been reported for the COVID-19 vaccines within the general population. Much of this information has been provided by the British HIV Association (2021) and the World Health Organization (2021), who have also indicated that HIV-infected people generally will likely produce a weaker response to the COVID-19 vaccines, but they are still expected to be protected from developing serious illness. This protection, however, may be to a lesser extent, especially for those individuals with low CD4+ counts (<100/mm³). Nonetheless, the U.K. Department of Health recommends that people with HIV, regardless of their CD4+ count, should receive a COVID-19 vaccine. In addition, because some people with HIV, especially those with a very low CD4 T-cell count, may be at increased risk for severe illness due to COVID-19, the CDC recommendation (CDC, 2020) advises that people with HIV may receive the vaccine as long as they do not have other conditions that would exclude them, such as a known severe allergic reaction or immediate allergic reaction of any severity after receiving a previous dose or to a component of the COVID-19 vaccine. The vaccines authorized for use in the United States and the United Kingdom do not contain live infectious virus so they are expected to be safe in people with low CD4 cell counts. It is a general rule that people with T-cell defects should not be given live vaccines, even though they are attenuated, so that they are supposed to only immunize the recipient and not cause disease. However, the attenuated pathogen in such vaccines could possibly mutate and revert to a more virulent form and cause serious disease in the immunocompromised host. Examples of this type of vaccine, that are currently used routinely, include the measles, chickenpox and one of the anti-shingles vaccines. This same concept applies for the COVID-19 viral vector vaccine products except they are not “true” live, attenuated vaccines, in the traditional sense. This is because the available ones now in widespread use, that are produced by Jannsen/Johnson & Johnson and Astra-Zeneca, consist of a live, but replication-incompetent, human adenovirus vector, encoding for the recombinant SARS-CoV-2 spike (S) glycoprotein, stabilized in its pre-fusion form. This differs from the vaccines produced by Pfizer and Moderna which use only synthetic mRNA as the immunogen. The viral vector’s purpose is to introduce the DNA, that encodes for the spike protein, into the human body in a somewhat unique way so that multiple
copies of it can be produced *in vivo*, over a short period of time, until the crippled virus immunogen is neutralized by the immune response that is being induced by the “replicating antigens” (R.J. North, personal communication) of SARS-CoV-2. This provides a persistent, albeit temporary, stimulus to the vaccinee. Given the strength and durability of this type of response, this usually means that, theoretically, and similar to what occurs with a truly live vaccine, a repeat (i.e., a booster) injection may not be necessary. As noted earlier, this consideration on whether to give boosters of the viral vector vaccine was being re-evaluated in October 2021 by the U.S. FDA and CDC, and starting in November 2021, a third (booster) injection is now highly recommended for most eligible people irrespective of what type of vaccine was previously given.

Additional features of the viral vector vaccine is that it is considered to be safe even for immunocompromised patients, including those with HIV/AIDS, given that the viral vector has been shown to be harmless in one of the most recently published studies on this topic (Hammer et al., 2013). Nonetheless, prior to this finding, there was some initial concern about a potential association observed more than a decade ago between adenovirus vector-based vaccines and an increased risk of acquiring HIV infection among men who received this type of vaccine (Buchbinder, McElrath, Dieffenback, & Corey, 2020, 18). This unexpected finding was detected in two HIV vaccine trials that used adenovirus vector containing products (Buchbinder et al., 2008; Gray et al., 2011) but these vaccines were constructed differently and are not related to the structure of the COVID-19 vaccines. The reason for this previously observed HIV risk remains uncertain, although several follow-up studies have suggested a possible interference in the HIV-specific vaccine response or in the CD4 cell susceptibility to HIV infection induced by this kind of vaccine as an unexpected side effect (Frahm et al., 2012; Perreau, Pantaleo, & Kremer, 2008). Accordingly, specific studies on this issue with this type of COVID-19 vaccine should be considered by closely monitoring the response patterns of HIV-infected people to various immune parameters that would include periodically measuring CD4 T cell counts, viral loads and anti-spike protein antibody levels subsequent to being vaccinated. In addition, testing for delayed-type hypersensitivity responses, as shown recently by Barrios et al. (2021) for recovering COVID-19 patients without HIV, may also provide valuable insights on the importance of cellular immune responses mediated by CD8+ T cells that directly kill virally infected cells as being an additional defense mechanism for prospective vaccine recipients. There are still, however, other unresolved issues. For example, will the currently available vaccines be fully protective against variants of SARS-CoV-2, especially the highly invasive/infectious Delta variant that was first identified in December 2020 (Nature, 2021; Torjesen, 2021), along with the Omicron variant with its peculiar set of mutations that was recognized and had spread to many countries in the latter part of 2021? What is the longevity of protection that is provided by any of these vaccines; and will additional boosters be needed beyond what is currently being done or recommended? In this regard, it is still unclear or not fully known how much SARS-CoV-2 antigen(s) is needed, or produced *in vivo* to induce an immune response that leads to optimal protection against COVID-19. Somewhat encouraging news, along these
lines, was recently reported (CNN, 2021) indicating that the Janssen/Johnson & Johnson vaccine provided lasting protection of at least 8 months duration and it afforded protection against the Delta and other variants. Although there had already been prior preliminary evidence (reviewed in Chen & Wherry, 2020) supporting an important role for both CD4+ and CD8+ T cells in the immunologic memory component in the host response to COVID-19, it is likely that additional related news on these topics will be forthcoming in the coming months. In light of these potential concerns/issues, it should be realized that, in the final analysis, the overall benefits of receiving any of the authorized COVID-19 vaccines in a pandemic situation currently outweigh the potential risks, even for people with impaired immune systems or other co-morbid conditions.

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The authors declare that they have no conflicts of interest. It should be noted that the citing of commercially available vaccine products should not be construed as an endorsement. They are being cited for the sole purpose of providing examples of vaccines that are in either the near-approval stage, have been approved or been given preliminary authorization for use for immunization purposes by authorizing/governmental agencies, after the manufacturers provided data showing that they have met the minimal standards for successfully completing and fulfilling the required clinical trial testing parameters for safety and efficacy.

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