BRITISH HIV ASSOCIATION GUIDELINES ON IMMUNISATION FOR ADULTS WITH HIV: SARS-CoV-2 (COVID-19) 2021

SARS-CoV-2 emerged at the end of 2019 as the cause of COVID-19 resulting in a pandemic. Data from observational studies indicate that a subset of people with HIV are at increased risk of severe COVID-19 outcomes. Opportunities should not be missed to offer immunisation against SARS-CoV-2 to people with HIV. Numerous vaccine candidates are in development and several have received authorisation in the UK and worldwide, although there is limited information that is specific to people with HIV.

These guidelines aim to provide information for healthcare professionals on the use of SARS-CoV-2 immunisation in people with HIV. They are based on the interpretation of current evidence, and will be kept under review and updated as new evidence emerges.

This consultation will be open until 5.00 pm on Friday 14 May 2021.

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SUMMARY OF RECOMMENDATIONS

Methodology: The British HIV Association (BHIVA) has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations [1,2]. See Appendices 1 and 2 for details of methodology and auditable outcomes.

Strength of recommendation (Grade 1 or 2)
1 = Strong recommendation to do (or not do) something: the benefits clearly outweigh the risks (or vice versa) for nearly all patients
2 = Weak recommendation: risks and benefits are more closely balanced or are more uncertain

Quality of evidence (Grade A–D)
A, B, C, D = High-, moderate-, low- and very low-quality evidence
A = Typically well-performed randomised controlled trials (RCTs) or other overwhelming evidence (such as well-executed observational studies with very large effects)
B = Typically randomised trials with important limitations (including well-performed RCTs with data that at the time of writing are available only via outputs from health authorities and as publication pre-prints prior to peer review) or other study designs with special strength
C = Typically observational studies or controlled trials with very serious limitations
D = Typically non-systematic observations, biological reasoning or observational studies with serious limitations

Good practice point (GPP): recommendation based on the clinical judgement and experience of the writing group

1. Data from observational studies indicate that a subset of people with HIV have an increased risk of severe COVID-19. Vaccination against SARS-CoV-2 is recommended for all people with HIV [Grade 1B].
2. Several SARS-CoV-2 vaccines have proved safe and efficacious in large clinical trials, and studies are ongoing to fully characterise their safety, tolerability, immunogenicity and efficacy. Although there are limited data in people with HIV, mRNA, adenovirus-vectored DNA, subunit (protein) and inactivated vaccines raise no safety concerns that are specific to people with HIV. The few contraindications (e.g. allergy to ingredients) are the same for people with and without HIV. These vaccines can be given regardless of treatment status, nadir and current CD4 cell count and current viral load [Grade 1B].
3. Although differences in efficacy cannot be excluded, there are no data currently to recommend one vaccine type over another for people with HIV, who are therefore advised to accept the first vaccine that is offered [Grade 1C]. *To be kept under review. Research need.*
4. People with HIV who have non-HIV-related risk factors for severe COVID-19 (including pregnant women) and those with HIV-related risk factors for severe COVID-19 (nadir CD4 count <200 cells/mm^3, current CD4 count <350 cells/mm^3 or ongoing viraemia) should not delay having the vaccine once offered and completing the recommended vaccine series [Grade 1B].
5. It is generally recommended that a vaccine series is completed using the same vaccine type and vaccine brand [Grade 2C]. Vaccine schedules that use different vaccine types (or possibly brands) for first and subsequent doses do not, at this time, raise recognised safety concerns and are being tested in clinical trials. In clinical practice, there may be circumstances in which a different vaccine type may be indicated for boosting, for example because a contraindication emerges after the first vaccine dose. There may also be circumstances in which the vaccine type or brand

used initially is not known; to reduce the likelihood of this, people receiving a SARS-CoV-2 vaccine should be advised to make a note of the vaccine type and brand received [GPP].

6. As with some other vaccines, some people with HIV might have HIV-related risk factors for a reduced immune response to SARS-CoV-2 vaccination, resulting in responses of lower magnitude and/or shorter duration. Although data are lacking, risk factors may include a nadir CD4 count <200 cells/mm^3, a current CD4 count <350 cells/mm^3, a low CD4/CD8 ratio or ongoing viraemia. These factors may lower the protection against SARS-CoV-2 especially after a single vaccine dose and in the case of virus variants that have reduced susceptibility to neutralising antibodies, and people with these risk factors should be counselled accordingly [GPP]. Vaccination is still likely to confer significant benefit and should not be contraindicated or deferred while waiting for immune reconstitution [Grade 1C]. Completion of the vaccine series is recommended to improve the response [Grade 1B]. At this time, for those who receive SARS-CoV-2 vaccination while immunosuppressed, repeat complete courses of vaccination after the CD4 cell count has improved with treatment is not indicated [Grade 2D]. *To be kept under review.*
7. Modified vaccine schedules (typically higher or increased number of doses) are sometimes used in people with HIV to increase response to vaccination. The number of SARS-CoV-2 vaccine doses and the interval between doses is currently dictated by national policy and cannot be personalised. There are no data at present to indicate how varying the SARS-CoV-2 vaccine schedule (number of doses and interval of dosing) may affect vaccine efficacy in people with HIV. *To be kept under review. Research need.*
8. People with HIV should be informed of the side effect profile of the administered vaccine and the typical course of vaccine-related side effects [GPP]. As monitoring vaccine efficacy is an important public health need, people with HIV should also be advised to seek medical attention and SARS-CoV-2 testing in the event of onset of symptoms suggestive of COVID-19 [GPP].
9. It is recommended that available information is provided to vaccine recipients about clinical studies on immunological and clinical efficacy of SARS-CoV-2 vaccination in people with HIV [GPP].
10. Outside of research studies, there is no indication at present for seeking SARS-CoV-2 antibody testing either pre- or post-vaccination to evaluate individual vaccine responses [Grade 2D]. Some but not all SARS-CoV-2 antibody tests available in routine diagnostic settings detect the anti-spike antibodies elicited by vaccination; studies are ongoing to evaluate anti-spike assays for their potential clinical utility in the vaccination setting. *To be kept under review.*
11. SARS-CoV-2 vaccination is still recommended in people with a previous COVID-19 diagnosis or positive SARS-CoV-2 antibody, RNA or antigen test [Grade 1B]. Although people with a previous diagnosis of SARS-CoV-2 infection or COVID-19 may have different vaccine requirements, it is not known whether these would apply equally to people with HIV, and completion of the full vaccine series is therefore recommended at this time, and is especially important for those with HIV-related risk factors for a reduced immune response [Grade 1C]. *To be kept under review. Research need.*
12. Although data are limited, it is generally recommended that in people with acute illnesses, including COVID-19, vaccination should be deferred until clinical recovery and to around 4 weeks after the first onset of symptoms. An interval of around 4 weeks after a first positive RNA or antigen SARS-CoV-2 test (for those with asymptomatic infection) is also suggested [Grade 2D].
13. Due to the lack of data on co-administration of SARS-CoV-2 vaccines with other vaccines, a minimum interval of 7 days is generally recommended before or after administration of any other vaccine. However, a risk–benefit assessment should guide practice [GPP].
14. After vaccination, people with HIV should be advised that the onset of protection after the first dose requires 2–3 weeks and that completion of the recommended vaccine series is needed to achieve higher protection [1B].
15. After vaccination, people with HIV should be advised to continue to follow general guidance to reduce risk (e.g. mask wearing, social distancing and handwashing), especially when in contact

with unvaccinated people [GPP]; the advice will evolve over time according to the epidemiological circumstances.

16. Passive immunisation with antibodies against the SARS-CoV-2 spike protein is currently being considered for the prophylaxis of SARS-CoV-2 infection (pre-exposure) and to prevent progression of an initial infection. The approach may be suitable for selected people with HIV (e.g. those who are profoundly immunosuppressed), but no recommendations are made at this time as such antibodies are not currently available outside of research studies. *To be kept under review.* There are no specific safety concerns preventing people with HIV from participating in ongoing studies on passive immunisation. To avoid potential interference with vaccine-induced immune responses, an interval of around 90 days is generally advised between receipt of SARS-CoV-2 antibodies (or convalescent plasma) and receipt of a SARS-CoV-2 vaccine [Grade 1C].

1. Introduction

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), a member of the *Coronaviridae* family, is a novel human virus that emerged at the end of 2019 as the cause of COVID-19 (coronavirus disease 2019), resulting in a pandemic. Coronaviruses (CoVs) are enveloped viruses with a positive-sense single-stranded RNA genome that cause infections in mammals and other vertebrates and derive their name from the halo of protein spikes covering their surface [3]. Common CoVs such as HCoV-229E and OC43 cause mild-to-moderate upper respiratory tract infections in humans [4]. Prior to the emergence of SARS-CoV-2, two related viruses, SARS-CoV and MERS-CoV, caused limited outbreaks of severe respiratory disease in humans [5]. Although the origin of SARS-CoV-2 remains unresolved, like SARS-CoV and MERS-CoV, it shares sequence homology with viruses circulating in bats in Southeast Asia [6]. Transmission from bats may have occurred via an intermediate mammalian host.

1.1 Transmission

SARS-CoV-2 is transmitted primarily through person-to-person contact via respiratory droplets and aerosols [3,7]. The risk of transmission is greatest in crowded indoor spaces or shared, poorly ventilated accommodation. In infected individuals, viral shedding starts in the pre-symptomatic phase and peaks 1 day before the onset of symptoms and into the first week of illness [3,8-10]. Although molecular assays performed on samples from the upper respiratory tract (nose, throat) remain SARS-CoV-2 positive for several days and sometimes weeks after symptom onset [9], shedding of viable, infectious virus is uncommon beyond day 9, although it may be longer in people with immune suppression [3,10]. Asymptomatic infections may be a source of transmission, especially after prolonged close contact [3]. SARS-CoV-2 remains viable on surfaces for several hours (porous materials) or several days (smooth hard surfaces); transmission can result from contact with contaminated surfaces (fomites) followed by touching of the eyes, mouth or nose [3]. SARS-CoV-2 is rapidly susceptible to inactivation; regular cleaning and disinfection of surfaces and good hand hygiene, alongside good ventilation, effectively reduce the likelihood of contact transmission. Despite faecal shedding, there is little evidence to suggest that the faecal–oral route plays an important role in transmission [3]. Vertical transmission has been rarely described.

1.2 Pathogenesis

Virus entry is mediated by binding of the viral spike to the metallopeptidase ACE2 (angiotensin-converting enzyme 2) on host cells. The spike is therefore the main target for neutralising antibodies, and its receptor-binding domain is a key immunogenic determinant. ACE2 is found on epithelial cells of the nose, mouth and pharynx, and is abundant in alveolar pneumocytes, vascular endothelium and enterocytes of the small intestine [11]. The wide distribution of ACE2, together with the immune and inflammatory reactions elicited by SARS-CoV-2 infection, explain the potential multi-system nature of COVID-19 [12]. The relationship between ACE2 levels, viral infectivity and severity of

infection is not well understood and knowledge of the relative contribution to disease of direct and indirect viral effects, including immune dysregulation and coagulopathy, is evolving. Current understanding is that pathogenesis is primarily driven by viral replication during the early phase of the infection, whereas disease results from exaggerated immune and inflammatory responses in the later phase [3].

1.3 Clinical presentation

Symptoms and severity vary, ranging from asymptomatic or pauci-symptomatic infections to severe infections characterised by pneumonia, acute respiratory distress syndrome, respiratory failure and multi-organ involvement with cardiovascular, thromboembolic, neurological and inflammatory complications, which may eventually cause death. The proportion of truly asymptomatic infections has not been conclusively established. Despite lack of symptoms, there may be imaging evidence of pneumonia [13]. The mean incubation period between exposure and appearance of symptoms is around 4–5 days (typical range 2–11 days). An influenza-like illness is the most common initial presentation; symptoms may include fever, cough, malaise, myalgia, headache, change in taste and smell, and gastrointestinal disturbance. Most symptomatic infections are of mild-to-moderate severity, and do not require hospital care [14]. Approximately 1 week after the onset of symptoms, there may be progression to a second phase of more severe and eventually critical disease. The overall infection fatality rate is estimated to be around 0.5–1% [15]. Hospitalised patients have a 5-fold higher mortality rate than that seen in patients hospitalised with influenza [16,17]. Laboratory abnormalities most commonly include lymphopenia, elevated serum aminotransaminase and lactate dehydrogenase levels and elevated inflammatory markers (e.g. C-reactive protein, erythrocyte sedimentation rate and ferritin) as well as abnormal coagulation test results.

The probability of serious COVID-19 disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions. A study conducted in the UK showed that the risk of death among patients ≥80 years was 20-fold higher than in those aged 50–59 years [18]. Comorbidities most commonly associated with severe COVID-19 include cardiovascular disease, type-2 diabetes and chronic lung disease. Other conditions that may increase risk include cancer, kidney disease, obesity (body mass index ≥30 kg/m^2), sickle cell disease, transplantation and other causes of immunosuppression. Pregnant women with SARS-CoV-2 infection, although less likely to manifest symptoms of fever and myalgia compared to non-pregnant women of reproductive age, are at an increased risk of severe COVID-19, particularly in later pregnancy [19]. The risk is further enhanced by pre-existing comorbidities, high maternal age and high body mass index. Preterm birth rates are also higher in pregnant women with COVID-19 than in pregnant women without the disease [19]. Black, Hispanic and South Asian individuals in the UK and the USA have been disproportionately affected, which is considered largely reflective of underlying socioeconomic disparities [18,20,21]. The impact of COVID-19 on long-term physical and psychological wellbeing after resolution of the acute phase is a field of ongoing study; people often report at least one persisting symptom 6 months after the initial infection (commonly described as 'long COVID-19') [22].

Effective therapeutic options are limited but evolving. The early phase of the infection is more likely to respond to antiviral therapies and anti-SARS-CoV-2 monoclonal antibodies, whereas the later stage may be responsive to immunosuppressive and anti-inflammatory therapies. Dexamethasone significantly reduces mortality in hospitalised patients with hypoxia, and corticosteroids are routinely recommended for those receiving supplemental oxygen and for ventilated patients [23,24]. Other treatment options include interleukin-6 receptor antagonists (tocilizumab and sarilumab). The RECOVERY trial has reported evidence of beneficial effects for the use of tocilizumab in those with COVID-19 who (i) require supplemental oxygen, (ii) show evidence of early phase hyperinflammatory status and (iii) are receiving concomitant corticosteroids [25]. The intravenous nucleotide analogue remdesivir is licensed for use in adolescents and adults with COVID-19 pneumonia requiring

supplemental oxygen. Remdesivir may shorten time to clinical recovery but no clear effect on the need for mechanical ventilation or overall mortality has been demonstrated; when used, it is typically reserved for hospitalised patients on minimal oxygen supplementation [26]. Studies are ongoing to test remdesivir in different populations, including pregnant women hospitalised with COVID-19 and patients with COVID-19 who do not require supplemental oxygen.

2. COVID-19 in people with HIV

There is no evidence that HIV increases the risk of SARS-CoV-2 transmission [27]. The clinical features of COVID-19 in people with HIV appear to be the same as in the general population [28], although there are no data on long COVID-19 in people with HIV. Early reports described no effect of HIV on COVID-19 mortality but more recent age-adjusted studies, including two from the UK, showed a higher risk of COVID-19 mortality among people with HIV [28-31], which was notable in age groups <60 years [28]. Whether this is driven by HIV *per se* rather than unmeasured or underestimated confounders associated with HIV status remains unclear. A large proportion of people with HIV are >50 years and have comorbidities; people with HIV who are obese or diabetic have been shown to be at risk for developing severe COVID-19 [28]. Studies to date have not fully adjusted for antiretroviral therapy (ART), CD4 cell count or viral load status, and for potentially important socioeconomic confounders such as occupation and housing. Notably, however, cellular immune deficiency and a low current or nadir CD4 cell count have been identified as potential risk factors for severe SARS-CoV-2 infection in people with HIV, irrespective of HIV virological suppression [32]. Taken together, these findings identify HIV infection as a risk factor for severe COVID-19 and suggest that the risk may not only reflect current suboptimal virological control and immune suppression, but also a history of previously significant immunosuppression. A further consideration is that persistent infection in severely immunocompromised individuals may allow the emergence of variant strains of SARS-CoV-2 with the potential to escape immune responses, particularly in the context of selective pressure from therapeutic intervention such as antibody therapies. It will be important to monitor emergence of SARS-CoV-2 variants in immunocompromised populations [33].

The management of COVID-19 in patients with HIV is the same as in patients without HIV. HIV should not be a reason to exclude a patient from otherwise indicated interventions or from clinical trials. In patients hospitalised with COVID-19, attention should be paid to ensuring that ART is continued and that concomitant medications, which are common in people with HIV, are reviewed, paying attention to potential drug–drug interactions. The clinical significance of the lymphopenia commonly seen in COVID-19 is at present unclear; absence of ACE2 in immune cells suggests that direct viral infection is unlikely to be the cause [11]. Prophylaxis for opportunistic infections should be considered where the CD4 cell count falls below recommended thresholds. It has been proposed that certain antiretroviral agents may modulate incidence or severity of SARS-CoV-2 infection; in a Spanish study, in a non-random sample of people with HIV, those receiving tenofovir disoproxil fumarate/emtricitabine were less likely to test seropositive for SARS-CoV-2 [27]. However, randomised trials will be required to confirm the observation. At present, there is no recommendation that antiretroviral regimens should be adjusted to reduce the risk of infection or following a diagnosis of COVID-19.

HIV testing should be offered to people whose HIV status is unknown when hospitalised with COVID-19.

3. SARS-CoV-2 vaccines

Numerous COVID-19 vaccine candidates are in development and several have received authorisation in the UK [34-36], Europe, North America and other countries worldwide. There are multiple vaccine platforms, with the most advanced including mRNA vaccines, adenovirus-vectored (Ad)-DNA vaccines and protein (subunit) vaccines. These vaccines express (mRNA and Ad-DNA vaccines) or contain (protein vaccines) the entire or parts of the spike protein. Available vaccines have been tested in many thousands of people in Phase 2 and Phase 3 trials and have been shown to be safe and

efficacious [37-42]. Reported vaccine efficacy against COVID-19 has ranged from ~50% to ~95% (Table 1). Emerging data indicate that there is also at least partial protection against SARS-CoV-2 infection (and therefore transmission), and that two-dose vaccine regimens start to confer substantial protection beginning from 2–3 weeks after the first dose [43,44].

Available vaccines have shown the promise of remarkable efficacy against severe COVID-19 (83–100%), hospitalisation and death (~100%). Not all studies have included sufficiently diverse populations in terms of age, ethnicity or range of underlying conditions and this may potentially limit the generalisability of efficacy conclusions. Longer-term follow-up data are also needed to determine the longevity of protection and the requirement for subsequent boosters. Early evidence suggests reduced efficacy of some vaccines against certain variant strains of SARS-CoV-2 [45,46], although prevention of severe disease may be preserved, including through the responses mediated by T cells [47]. SARS-CoV-2 will continue to evolve and vaccines may need to be adapted over time. Second-generation versions of available vaccines are already in development and additional vaccine platforms are being explored.

When comparing vaccine efficacy figures, it should be noted that (i) no direct head-to-head comparisons have been performed, (ii) definitions of efficacy are similar but not entirely consistent across studies and (iii) pivotal trials have been conducted in different epidemiological settings particularly when considering circulation of novel virus variants. Furthermore, data on efficacy and safety of available vaccines are currently largely derived from interim analyses of ongoing studies, only a subset of which has been published after peer-review. Documents related to the authorisation by the European Medicines Agency (EMA), US Food and Drug Administration (FDA) or the UK Medicines & Healthcare products Regulatory Agency (MHRA) are also available for review.

Table 1. Characteristics of main available SARS-CoV-2 vaccine types

Company	Vaccine	Platform	No. of doses	Interval between doses	Overall efficacy[a,b]	People with HIV in pivotal studies
Pfizer BioNTech	BNT162b2	mRNA in lipid nanoparticle	2	Pfizer: 3 weeks UK: at least 3 weeks	95%	Yes (<200)
Moderna	mRNA-1273	mRNA in lipid nanoparticle	2	4 weeks	94%	Yes (<200)
Oxford AstraZeneca	ChAdOx1 AZD1222	Non-replicating chimp Ad-vectored DNA	2	4–12 weeks Greater efficacy with interval >6 weeks	~60%[c]	Yes
Johnson & Johnson	JNJ-78436725	Non-replicating human Ad26-DNA	1	–	66–67% USA 72–74% Latin America 66–68% South Africa 52–64%[d]	Yes (~1200)
Gamaleya	Sputnik V	Non-replicating human Ad26-DNA and Ad5-DNA	2	3 weeks	92%	No
Novavax	NVX-CoV2373	Recombinant spike protein nanoparticle + Matrix M-1 adjuvant	2	3 weeks	UK 89% South Africa 49–60%[d,e]	Yes (~260)

[a]Data are largely derived from interim analyses and only a subset has been published; please refer to the MHRA website for additional information on vaccines authorised in the UK. [b]In most studies, overall efficacy defines protection (versus control) against symptomatic SARS-CoV-2 infection (including mild, moderate or severe/critical forms of COVID-19) occurring at least 7 or at least 14 days after completion of the vaccination series among people without prior SARS-CoV-2 infection; the pivotal study of the JNJ-78436725 vaccine used moderate to severe/critical COVID-19 occurring at least 14 days and at least 28 days after vaccination as the

co-primary endpoint. [c]Vaccine efficacy with an interval of 4–12 weeks between two standard doses; the vaccines showed no efficacy in protecting against mild-to-moderate SARS-CoV-2 infections in South Africa; see text for additional information on efficacy. [d]>90% of SARS-CoV-2 infections due to B1.351 variant; [e]range describes efficacy when including or excluding people with HIV.

Chinese companies have developed two inactivated virus vaccines (Sinovac/CoronaVac and Sinopharm BBIBP-CorV) which have been granted approval in several countries. These vaccines adopt a more traditional approach by using chemically killed viral particles to induce an immune response. Reported efficacy of CoronaVac against symptomatic SARS-CoV-2 infection has varied across sites, ranging from 50% in Brazil to 65% in Indonesia and 91% in Turkey, whereas 70–86% efficacy has been described for the Sinopharm vaccine; the studies excluded people with HIV. Publication of peer-reviewed data is awaited.

3.1 mRNA vaccines

The initial concept of mRNA vaccines was introduced in the 1990s, followed by explorative research applications in the field of cancer and infectious diseases. To date, two mRNA vaccines against COVID-19 have been authorised for use in the UK, BNT162b2 (manufactured by Pfizer) [34] and mRNA-1273 (manufactured by Moderna) [35]. Both contain synthetic single-stranded RNA molecules encapsulated within a nanoparticle. After uptake in the host cell cytoplasm, ribosomes translate the mRNA into the corresponding protein. BNT162b2 encodes the receptor-binding domain of the spike protein of SARS-CoV-2, whereas mRNA-1273 encodes the spike protein stabilised in its prefusion conformation. The mRNA does not enter the cell nucleus, does not interact with the host cell DNA and does not amplify inside the cell. It is degraded soon after translation in the cytoplasm by normal intracellular processing mechanisms. The protein produced from the mRNA is processed into peptides for presentation at the cell surface in the context of MHC class I and class II, triggering an immune response that includes neutralising antibodies and T-cell responses [47]. Although there are some differences in the T-cell responses induced by BNT162b2 and mRNA-1273, both mRNA vaccines are highly immunogenic, inducing higher post-vaccination neutralising antibody levels than measured in convalescent plasma, and affording high efficacy against COVID-19 [37-40]. These vaccines might retain substantial activity against emerging virus variants [48,49], but additionally offer the advantage that the platform can be rapidly adapted to targeting novel virus strains by altering the mRNA code in the vaccine to reflect that of the variant strain. In supplemental analyses of the pivotal trials of BNT162b2 and mRNA-1273, vaccine efficacy among subgroups defined by parameters such as age, sex, race, ethnicity and presence of a coexisting condition (including stable HIV infection) was generally consistent with that observed in the overall population [37-40].

Local site reactions and systemic events (primarily fatigue and headache, but also myalgia, joint pain, chills and fever) are common after vaccination but are short-lived (1–3 days) and usually mild-to-moderate in severity [37-40]. Adverse reactions occur more commonly in younger people and after the second dose. Severe allergic reactions have been reported (~11 cases per 1 million vaccinations), including less commonly cases of anaphylaxis [50]. Most cases of anaphylaxis occur within the first 15 minutes after administration. mRNA vaccines are contraindicated in people with hypersensitivity to the active substance or to any of the excipients. Of interest, there have been a few reports of transient (~10 days) lymphadenopathy (e.g. axillary swelling and tenderness), which may be related to vaccination. Cases of Bell's palsy have also been observed but relatedness has not been established. Transient, usually mild, decreases in lymphocyte counts 1–3 days after vaccination are a commonly observed laboratory abnormality.

3.2 Adenovirus-vectored DNA vaccines

Replication-deficient Ad vectors lack the early *E1A* and *E1B* genes, which are essential for reproduction of the adenovirus [51], and deliver the DNA encoding the spike protein without replicating in the vaccinated individual. Neither the vector nor the DNA interact with host cell DNA.

The expressed antigen stimulates protective neutralising antibodies and T-cell immune responses. Authorised and candidate Ad-vectored SARS-CoV-2 vaccines use either a chimpanzee (ChAd) or a human Ad vector (Ad5 or Ad26) (Table 1). The technology employed by the Johnson and Johnson JNJ-78436725 vaccine is also used in their EMA-approved Ebola vaccine (Ad26.ZEBOV). Pre-existing or newly induced immunity against adenovirus can hinder efficacy of Ad-vectored vaccines, and limit the applicability of frequent boosters with the same vaccine type. This concern has informed the vaccine development strategy for both the AstraZeneca ChAdOx1 vaccine, where a chimp, rather than human, Ad vector is used ensuring low risk of pre-existing immunity in the population, and the Gamaleya Sputnik V vaccine where different Ad vectors are used for priming and boosting. Studies are ongoing to test using different vaccine brands for priming and boosting.

The ChAdOx1 vaccine has so far been studied in four ongoing randomised, blinded, controlled clinical trials including: COV001 – a Phase 1/2 study in healthy adults aged 18–55 years (UK); COV002 – a Phase 2/3 study in adults aged ≥18 years including the elderly (UK); COV003 – a Phase 3 study in adults aged ≥18 years including the elderly (Brazil); and COV005 – a Phase 1/2 study in adults aged 18–65 years (South Africa). A pooled interim analysis showed that a two-dose vaccine series was safe and effective against symptomatic SARS-CoV-2 infection [41]. Only COV002 and COV003 exceeded the threshold of ≥5 virologically confirmed COVID-19 symptomatic cases per study and therefore contributed to the pooled efficacy analysis. There were differences in dose levels (a subset received a low priming dose by error, followed by a standard dose booster) and the interval between doses varied across the trials (ranging from 3 to 23 weeks), which complicates the interpretation of the pooled analysis. Furthermore, most participants were of white ethnicity and the number of older patients was relatively small; currently available clinical trial data do not allow an estimate of vaccine efficacy in subjects over 55 years of age. Additional studies are underway to address these uncertainties. In a further analysis, among 17,177 trial participants who were SARS-CoV-2 seronegative at baseline (8948 in the UK, 6753 in Brazil and 1476 in South Africa), overall vaccine efficacy against symptomatic COVID-19 was 66.7% across different dosing groups [43]. Vaccine efficacy was 63% among those who received two standard doses and 81% among those who received a low priming dose followed by a standard booster dose. In the standard dose–standard dose group, vaccine efficacy was 82% when the time between doses was ≥12 weeks and 55% when the time between doses was ≤6 weeks. Efficacy after a single standard dose was 76% in the 90 days following vaccination. Current data support dose intervals from 8 to 12 weeks, however the data for longer intervals are limited. Whereas trial data are limited in older adults, high seroconversion rates were observed in people aged ≥65 years following the first (97.8%; *n*=136) and the second recommended dose (100.0%; *n*=111) of ChAdOx1 [36].

The safety assessment of ChAdOx1 is based on an interim analysis of pooled data from the trials [36,45]. The most frequently reported adverse reactions included local site reactions and systemic events (primarily fatigue and headache, but also malaise, myalgia, joint pain, chills, fever and nausea) that were usually mild to moderate in severity and resolved within a few days. Adverse reactions were more common in younger people and milder and reported less frequently after the second dose. Three cases of transverse myelitis occurred in the trials, two of which were in the vaccine arm. More recently, attention has focused on the rare occurrence of thromboembolic events accompanied by thrombocytopenia among recipients of the ChAdOx1 vaccine, although a causal link has not been determined and the benefits of vaccination continue to outweigh any risk [52]. Of note, numerical imbalances in the occurrence of thromboembolic events between vaccine and placebo recipients were observed in the pivotal JNJ-78436725 study, alongside seizures and tinnitus [53].

4. General indications

In the UK, SARS-CoV-2 vaccines are allocated according to priority lists based on risk of occupational exposure and risk of severe disease [54], followed by a gradual extension to the rest of the

population. The choice between vaccines is based on availability. BNT162b2 is currently authorised for use in people aged ≥16 years; mRNA-1273 and ChAdOx1 are currently authorised for use in those aged ≥18 years. Some countries have applied upper or lower age restrictions to the ChAdOx1 vaccine. The ChAdOx1 vaccine has fewer logistical constraints for distribution, as it can be stored and distributed at 2–8^{0}C (in contrast to BNT162b2 and mRNA-1273 which must be stored frozen). There are no data on the interchangeability of vaccines and the same vaccine type and brand is recommended for completion of a vaccination series. A previous history of confirmed or suspected infection with SARS-CoV-2 does not contraindicate vaccination and pre-vaccination serological testing is not required or recommended at present. Pregnancy or breastfeeding are not absolute contraindications to vaccination with available SARS-CoV-2 vaccines [55]. Given the increased risk of severe COVID-19, the decision should be made on a case-by-case basis, taking into account the woman's risk and preferences. Among available vaccines, BNT162b2, mRNA-1273 and JNJ-78436725 have reported no adverse findings in non-clinical reproductive developmental toxicity studies, whereas data for ChAdOx1 are pending; these vaccines cannot cause genetic changes to the fetus. Pregnancy exposure registries have been set up to monitor pregnancy outcomes in women exposed to COVID-19 vaccines during pregnancy.

5. SARS-CoV-2 vaccines in people with HIV

Some, but not all, pivotal clinical trials of authorised and candidate vaccines have included people with HIV (Table 1), restricting eligibility to those with stable, well-controlled infection and excluding people with significant immunosuppression. The pivotal BNT162b2 and mRNA-1273 trials [37-40] included a small number of people with HIV, and no unusual safety concerns were reported in this group. However, the available data are insufficient to allow separate analyses of safety or efficacy specifically for people with HIV [56]. It is encouraging that the trials did not see a marked decline in vaccine efficacy or adverse safety signals in overall analyses of people with underlying medical conditions. The ChAdOx1 studies recruited people with HIV, however subanalysis results are not available at present. Press-released data from the Novavax vaccine studies provide some preliminary as yet unpublished information. In an interim analysis of the Phase 3 clinical trial conducted in the UK, vaccine efficacy against symptomatic SARS-CoV-2 infection was 89% among more than 15,000 participants [57]. In the Phase 2b clinical trial conducted in South Africa, in which 6% (~260) of more than 4400 participants had stable, well-controlled HIV infection, an interim analysis showed a vaccine efficacy of 60% (95% confidence interval [CI] 19.9–80.1) when excluding participants with HIV, and 49% (95% CI 6.1–72.8) when including participants with HIV. Preliminary sequencing data showed that ~93% of the cases of COVID-19 occurring after vaccination were due to the variant B.1.351. These preliminary data suggest, but do not demonstrate, that HIV infection may reduce the efficacy of the Novavax vaccine against variants with reduced susceptibility to antibody-mediated neutralisation. Publication of peer-reviewed data is awaited to determine the cause of the described decline in vaccine efficacy when excluding or including ~260 people with HIV. The pivotal trial of the JNJ-78436725 vaccine included a proportion (2.8%; n=1218) of patients with known, stable HIV infection, of whom 601 received a single dose of the vaccine and 617 received placebo [58]. Of note, trial participants with no comorbidities and no medical history of HIV were not tested for HIV infection. Among people with known HIV who received the vaccine, there were five cases of moderate-to-severe/critical COVID-19 with onset at least 14 days after vaccination and two cases with onset at least 28 days after vaccination. In those participants with HIV who received placebo, there were five and four cases respectively. These figures give no evidence of vaccine efficacy at least 14 days after vaccination, whereas vaccine efficacy was 48% after at least 28 days, but the very large confidence intervals around these estimates preclude definite conclusions.

Thus, for available SARS-CoV-2 vaccines, there are no available data to inform understanding of the absolute and comparative immunological and clinical efficacy in people with HIV or the impact of different vaccine dosing schedules in this population. While antibody levels may not be reliable markers for overall immunity [59], people with HIV are at risk of reduced responses to vaccination,

with blunted antibody and T-cell responses that may decline more rapidly than in people without HIV [60-62]. These effects may translate into:

- Lower vaccine efficacy, particularly against virus variants with reduced susceptibility;
- Shorter duration of protection;
- Potential requirement for additional or higher vaccine doses.

HIV-related parameters, comprising current and nadir CD4 cell count and other markers of immune dysfunction such as a low CD4/CD8 ratio, ART use and plasma viral load, are likely to modulate these hypothetical effects [60-63]. More than 40% of people with HIV in the UK are aged ≥50 years and increasing age may affect the overall immunological and clinical efficacy of vaccination. Whereas people with a previous SARS-CoV-2 infection may have different and potentially reduced vaccination requirements, it is not known whether this may apply to people with HIV as responses to SARS-CoV-2 may be blunted or short-lived in some. The risk of re-infection is extremely low in the 90 days after confirmed SARS-CoV-2 infection, indicating that it might be safe to postpone vaccination [64]. However, the duration of protection after SARS-CoV-2 infection is not known in people with HIV and may be reduced to less than 90 days. It might also be difficult to access the vaccine again if initially declined.

Based on the reported excess COVID-19 mortality risk, people with HIV are to be prioritised for COVID-19 vaccination: all people with HIV are in the Joint Committee on Vaccination and Immunisation (JCVI) priority group 6 (which also includes people with other conditions associated with worse outcomes such as diabetes); those considered clinically extremely vulnerable (which includes people with CD4 count <50 cells/mm^3, an opportunistic infection in the previous 6 months, or significant multi-morbidity), as per guidance from BHIVA, are advised to be included in priority group 4 [65].

6. Ad-vectored vaccines and HIV acquisition

Concerns regarding the use of Ad vectors, specifically Ad5, for COVID-19 vaccine development have been raised in relation to a potential increased risk of HIV acquisition [66]. The STEP and Phambili trials, completed over a decade ago, evaluated an Ad5-vectored HIV vaccine for efficacy against HIV acquisition. Both studies reported an increased risk of HIV acquisition among vaccinated men. In the STEP trial, men who were Ad5 seropositive and uncircumcised at enrolment were at elevated risk of HIV acquisition in the first 18 months after vaccination, compared to the placebo group (5.1% *vs* 2.2% per year for Ad5-seropositive men and 5.2% *vs* 1.4% for uncircumcised men, respectively) [67]. The effect was shown to wane over time [68]. Although it remains incompletely understood why Ad5 seropositivity was associated with an increased risk of HIV infection after penile exposure, it has been proposed that the effect may be related to the immune response towards the Ad5 vector, which might have dampened protective immune responses against HIV, while at the same time enhancing HIV replication and transmissibility [69,70]. Supporting the results of the STEP trial, infection of rhesus macaques with Ad5 followed by immunisation with a replication-incompetent Simian immunodeficiency virus (SIV)/Ad5 vaccine increased the risk of SIV acquisition from a low-dose SIV penile challenge [71]. These findings raise concerns that Ad5-vectored DNA vaccines developed against SARS-CoV-2 could potentially increase the risk of HIV acquisition in men who receive the vaccine, especially in high HIV prevalence areas. The potential increased susceptibility to HIV has been acknowledged, with emphasis placed on monitoring participants in Phase 2/3 studies. There is no evidence currently of increased risk of HIV acquisition for other Ad vectors, although possible cross-reactivity has been described. Due to lack of experimental evidence it is important that these hypothetical risks and uncertainties are discussed in full with trial participants to enable an informed decision.

7. Passive immunisation: monoclonal antibodies for the prophylaxis of infection and disease progression

Virus-neutralising monoclonal antibodies targeting different epitopes of the spike protein have been developed against SARS-CoV-2 and are at various stages of clinical development to ascertain their efficacy after a single intravenous infusion in individuals at risk of severe COVID-19 outcomes [72,73]. Three leading candidate monoclonal antibody preparations are shown in Table 2. Potential uses include (i) pre-exposure prophylaxis (where vaccines may not be expected to be efficacious) and (ii) prevention of disease progression in the early stages of the infection, when administered as soon as possible after a positive SARS-CoV-2 detection test and within 10 days of symptom onset. Efficacy data from trials suggest that monoclonal antibodies may have a role in protecting people at high risk of developing severe disease, although logistic constrains may be substantial; the definition of high risk is broad, and includes those with immunosuppressive disease, but data pertaining to people with HIV specifically are not available. One concern is the potential for virus immune evasion, which might be expedited by selective pressure from monoclonal antibodies. To overcome this, some monoclonal antibody preparations combine two separate antibodies targeting distinct, non-overlapping spike protein epitopes. Viral escape would thus require simultaneous advantageous mutations in genetically distinct areas. Efficacy trials of monoclonal antibodies in different patient groups and settings are ongoing and initial positive results have been reported for treatment in early SARS-CoV-2 infection [74,75].

Table 2. Monoclonal antibodies against SARS-CoV-2 for prophylaxis against infection (pre-exposure) and disease progression (in early infection)

Brand	Antibodies	Comments
Regeneron REGN-COV2[a]	Casirivimab + imdevimab	Used in combination
Eli Lilly	Bamlanivimab +/- etesevimab	Used alone or in combination
AstraZeneca AZD7442	AZD8895 + AZD1061	Engineered to extend half-life to 6–12 months after a single administration

[a]REGN-COV2 has received authorisation from both the EMA and the FDA, but is not yet authorised in the UK.

8. Communication and information sharing with people with HIV

There is limited information about COVID-19 vaccines for people with HIV, and these guidelines are based on the interpretation of current evidence. BHIVA has regularly issued statements and will continue to do so as new information becomes available. These statements can be accessed via the BHIVA website: https://www.bhiva.org/Coronavirus-COVID-19.

People with HIV will have questions about COVID-19 and about SARS-CoV-2 vaccination, and emerging evidence will lead to new questions. It is vital to engage with people with HIV to answer questions and address concerns, as well as to educate and correct misinformation. It is also important to educate health workers (doctors, nurses, pharmacists, health advisers, carers and social workers) and others concerned with the care and support of people with HIV; they need to take a proactive role in discussions about SARS-CoV-2 vaccines.

Peer support and other organisations can also fulfil a useful role. BHIVA is working with the UK Community Advisory Board (UK-CAB) and HIV i-Base to update an online question and answer (Q&A) resource that uses non-technical language. This can be accessed at: https://i-base.info/ and https://i-base.info/qa/. The HIV i-Base resource is updated regularly and submission of questions and feedback is welcomed from both health workers and the community.

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Appendix 1 Methodology for guideline development

The draft guidelines were developed using the methodology outlined in the BHIVA guideline development manual (see https://www.bhiva.org/file/jgCacHqmuxZFL/GuidelineDevelopmentManual.pdf), and based on seven core principles:

- Development was carried out by nationally representative experts in the field of HIV medicine who are free of overt conflicts of interest.
- The expert group performed a systematic review to identify and critically appraise the evidence for the patient population (people with HIV), with a focus on vaccination as the intervention including an appraisal of risk–benefit, people not known to have HIV as the comparison, and vaccine efficacy against COVID-19 of any severity as the outcome (i.e. population, intervention, comparator and outcome [PICO] strategy). Given the rapidly evolving field, evidence taken into account included press releases, pre-prints and documentation made available by health authorities; the limitations of non-peer-reviewed evidence were fully considered and highlighted.
- Recommendations were explicitly linked to the supporting evidence using the GRADE system. Based on the GRADE instrument, the co-authors independently scored and then discussed and reached a consensus on the strength of recommendation (1 or 2) and level of supporting evidence (A–D). The recommendations result from a collective decision reached after discussion by the expert co-authors within the writing group.
- The language/terminology is in accordance with NHIVNA Best Practice recommendations: http://www.hivnursing.net/media/1561113450HIV-19-BP1%20mod.pdf.
- Recommendations take into account equality issues, financial and resource implications, and patient choice and lifestyle.
- The guidelines are person-centred and, in line with BHIVA standards, consider the psychological aspects of living with HIV, where appropriate.
- Peer review was sought from two independent advisors, subject to the same policy on disclosure of conflicts of interest as the writing group. Initial feedback was also sought from the BHIVA Guidelines Subcommittee and the BHIVA Executive Committee. The Chair of the writing group incorporated the initial comments and feedback into the revised draft, prior to the release of the draft recommendations for public consultation, including the full membership of BHIVA, BHIVA-invited stakeholders, service users, patients and interested members of the general public.

Appendix 2 Auditable standards

1. Proportion of people with HIV who have a record of their SARS-CoV-2 vaccination history in the HIV medical record (including offer of vaccine; whether offer accepted or declined with reasons for declining; date of vaccination; vaccine type if known; any adverse events of vaccination with time of onset, character and duration; number of doses received. Target >85%.
2. Proportion of people with HIV who have risk factors for severe COVID-19 or reduced vaccine response who have a record of a discussion around these predictors and their potential implications documented in the medical record. Target >85%.
3. Proportion of people with HIV who have a record of a discussion around the side effects of SARS-CoV-2 vaccination where appropriate and the need to seek medical care and SARS-COV-2 testing in case of symptoms suggestive of COVID-19 occurring after receiving SARS-CoV-2 vaccination. Target >80%.