

SARS-CoV-2 immunity and vaccine strategies in people with HIV

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SARS-CoV-2 Immunity and Vaccine strategies in PLWH1
2 30
34 31 **Abstract**

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6 32 Current SARS-CoV-2 vaccines, based on the ancestral Wuhan strain, were developed rapidly to meet the needs
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8 33 of a devastating global pandemic. People living with HIV (PLWH) have been designated as a priority group for
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10 34 SARS-CoV-2 vaccination in most regions and varying primary courses (2 or 3-dose schedule) and additional
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12 35 boosters are recommended depending on current CD4+ T cell count and/or detectable HIV viraemia. From the
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14 36 current published data, licensed vaccines are safe for PLWH, and stimulate robust responses to vaccination in
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16 37 those well controlled on antiretroviral therapy and with high CD4+ T cell counts. Data on vaccine efficacy and
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18 38 immunogenicity remain, however, scarce in PLWH, especially in people with advanced disease. A greater
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20 39 concern is a potentially diminished immune response to the primary course and subsequent boosters, as well
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22 40 as an attenuated magnitude and durability of protective immune responses. A detailed understanding of the
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24 41 breadth and durability of humoral and T cell responses to vaccination, and the boosting effects of natural
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26 42 immunity to SARS-CoV-2, in more diverse populations of PLWH with a spectrum of HIV-related
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28 43 immunosuppression is therefore critical. This article summarises focused studies of humoral and cellular
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30 44 responses to SARS-CoV-2 infection in PLWH and provides a comprehensive review of the emerging literature
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32 45 on SARS-CoV-2 vaccine responses. Emphasis is placed on the potential effect of HIV-related factors and
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34 46 presence of co-morbidities modulating responses to SARS-CoV-2 vaccination, and the remaining challenges
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36 47 informing the optimal vaccination strategy to elicit enduring responses against existing and emerging variants
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38 48 in PLWH.

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45 49 **Lay Abstract**

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47 50 People living with Human Immunodeficiency Virus (PLWH), appear to be at a higher risk (approximately 15%)
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49 51 of becoming more seriously unwell if they are infected with severe acute respiratory syndrome coronavirus-2
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51 52 (SARS-CoV-2), the virus that causes COVID-19 disease, and at least twice as likely to die from COVID-19 as the
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53 53 rest of the population. SARS-CoV-2 vaccination and boosters are recommended for all PLWH. However, there
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55 54 is limited information about the protective immune responses to both vaccination (and actual infection), the
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2 55 protection against serious COVID-19 disease, and whether the safety profile of the vaccines, which are very
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4 56 safe in the general population, differs in PLWH. Here we summarise findings from studies which looked
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6 57 specifically at vaccine-related immune responses in PLWH, and discuss factors – such as age, known to impact
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8 58 negatively on immune responses in the general population, to see whether this effect is worse in PLWH. A
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11 59 better understanding of these issues will help guide tailored vaccination and prevention strategies for PLWH.
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61 **Introduction**

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21 62 Coronavirus Disease (COVID-19), caused by SARS coronavirus 2 (SARS CoV-2), emerged in late 2019, and was
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23 63 declared a global pandemic by the World Health Organisation (WHO) in March 2020. As of December 2021,
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25 64 >277 million cases and >5 million deaths had been reported, almost certainly a significant under-estimation of
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27 65 the true numbers, and have led to significant pressures and disruption of local, national and international
28
29 66 healthcare systems [1]. It has been estimated that PLWH represent approximately 1% of total hospitalised
30
31 67 cases [2]. However, the actual prevalence of SARS-CoV-2 infection could be higher in low and middle-income
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33 68 countries where access to diagnosis is limited, and HIV burden is much higher. With nearly 40 million PLWH
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35 69 and 12.6 million people not under suppressive antiretroviral therapy (ART)[3], the dynamics of co-existing
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37 70 SARS-CoV-2 infection require a syndemic understanding of health and disease.
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43 72 Unlike HIV infection, which in the absence of ART is invariably fatal, the course of COVID-19 disease is highly
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45 73 variable. The majority of cases are either asymptomatic or mildly symptomatic with cough, upper respiratory
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47 74 symptoms, myalgia and headache, but some progress to a potentially fatal condition of acute respiratory
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49 75 distress syndrome, septic shock, and multiorgan failure [4] [5] [6]. There is an exponential increase in mortality
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51 76 with increasing age [7] and there is a clear correlation between risk of severe disease and comorbidities
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53 77 including hypertension, diabetes, cardiovascular and respiratory disease [8] [9]. PLWH have a higher burden
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2 78 of these disease risk factors than the general population. Furthermore, PLWH are an ageing population, with
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4 79 nearly half of the PLWH in the U.S. being >50 years of age, which is set to increase [10, 11].
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7 80 Immunosuppressed patients, including people with haematological malignancies [12], solid organ transplant
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9 81 recipients [13] and those on chronic oral glucocorticoids for rheumatic conditions[14] have also been identified
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11 82 as being at high risk for severe COVID-19 disease. Similarly, PLWH have been included among those deemed
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13 83 vulnerable to worse outcomes from SARS-CoV-2 infection [15]. Large cohort studies from the UK, South Africa,
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15 84 the US and data reported to the WHO from across the world have identified a higher risk of death and
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17 85 hospitalisation from COVID-19 disease in PLWH [16-19]. There is also evidence for a more severe course of
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19 86 COVID-19 disease in people with cellular immune deficiency and a lower CD4+ T cell count/low CD4+ T cell
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21 87 nadir [20-22]. As a result, SARS-CoV-2 vaccination is recommended by national and international HIV societies
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23 88 for PLWH [15, 23, 24]. An informal poll of more than 100 countries from all regions, performed by the WHO,
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25 89 showed that at least 40 countries have an immunisation policy that prioritises vaccinations for PLWH [25]. In
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27 90 general, PLWH and especially those with a CD4+ T cell count <350 cells/ μ L or ongoing viraemia, are advised to
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29 91 have three doses of vaccine as part of their primary vaccination course [23, 24]. Given that sub-optimal
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31 92 responses to several other vaccines have been reported in PLWH [26] this raises concerns about the potential
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33 93 efficacy of SARS-Cov-2 vaccines in this potentially more vulnerable population. Additional vaccine doses are
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35 94 expected to increase responses in this group, reflected in recommendations by most Western countries, the
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37 95 US and the UK, advising a first booster (fourth dose) and second booster (fifth dose). These guidelines are
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39 96 regularly updated in line with the evolving pandemic response [27].
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46 97 Here, we review the complex interplay between HIV and SARS-CoV-2 infection in adults and summarise the
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48 98 knowns and many unknowns of COVID-19 vaccine responses in the setting of HIV infection.
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99 Immune correlates of protection against SARS-CoV-2 infection

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55 100 Increased understanding of protective immune responses against SARS-CoV-2 infection and disease
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57 101 progression have provided valuable insights for the development and evaluation of vaccines. The humoral
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2 102 immune response to natural infection and vaccination against SARS-CoV-2 has received a lot of attention.
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4 103 Following infection with SARS-CoV-2, a specific humoral response is initiated [28]. Importantly, IgG antibodies
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6 104 which bind to spike protein, particularly the receptor binding domain (RBD), are more likely to be neutralising
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8 105 and these have been linked to viral clearance in patients who have recovered from SARS-CoV-2 infection [29].
9
10 106 Non-human primate (NHP) models illustrated protection from reinfection and total protection provided by
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12 107 passive transfer of neutralising antibodies [30-32]. Indeed, studies in humans have shown that higher anti-
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14 108 spike IgG and neutralising antibody titres generated following natural infection or vaccination are associated
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16 109 with a lower risk of reinfection [33], symptomatic disease [34] and a positive correlation between clinical
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18 110 severity and SARS-CoV-2 specific antibodies [35]. There is evidence that the timing of IgG anti-spike response
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20 111 may be a critical determinant in survival; Lucas *et al* showed that deceased patients mounted a robust, specific
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22 112 response, with neutralising antibodies. However, it was a delay in seroconversion that resulted in poor viral
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24 113 control in these patients [36]. Many studies have also evaluated the impact and timing of serum IgM and IgA
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26 114 specific antibodies [37] which have been related to serological diagnosis and prognosis prediction rather than
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28 115 protective effects [38-40]. Although these specific antibody responses can be detected within 2 weeks of initial
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30 116 infection [41, 42], it has been well-documented that humoral immune responses to coronaviruses are variable
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32 117 and short-lived; levels decay post-infection and vaccination after approximately the first month, with a half-
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34 118 life of approximately 2 months [43, 44]. The level of neutralising antibodies required for continuing protection
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36 119 following natural infection or vaccination has not yet been determined; this is further complicated by the
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38 120 emergence of variants of concern (VOC) which have mutations/deletions to the spike protein, particularly in
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40 121 the RBD, which can impact neutralising sensitivity [45]. This is an important consideration as all of the currently
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42 122 licensed SARS-CoV-2 vaccines are based on the original Wuhan strain [46-48]. Khoury *et al* developed a
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44 123 predictive model that suggests there is a proportionate response of neutralisation titres whereby the lower
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46 124 the initial response to wild type virus, the greater the impact on vaccine response to other strains [49]. Several
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48 125 studies have shown continued protection against variants following vaccination persisting for approximately 6
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50 126 months with implications for the timing of boosters [50-52]. Although antibody responses wane, class switched
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2 127 spike-specific and RBD-specific memory B cells can provide a long-lived memory pool that can react rapidly
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4 128 upon reinfection or vaccine boosting [53]. Spike-specific memory B cells have been shown to persist for 6
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6 129 months to a year following infection [54, 55], with evidence of higher levels of somatic hypermutation, higher
7
8 130 binding affinity and neutralising capacity [56, 57]. Memory B cell responses may even be of higher quality
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10 131 following mild compared to severe SARS-CoV-2 infection, producing more robust responses [58], even when
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12 132 neutralising antibodies were undetectable. However, recall responses of RBD-specific memory B cells has been
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14 133 shown to decline with age [53] [59].
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18 134 Increasing evidence supports a protective role versus pathogenic role of T cell immunity against SARS-CoV-2
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20 135 infection [60]. Although the characterisation of virus-specific T cell responses is more technically challenging,
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22 136 an early development of a cytotoxic CD8+ T cell response is associated with significantly milder disease [61-64]
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24 137 and accelerated viral clearance [65-68]. Further indirect evidence of the importance of T cell responses comes
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26 138 from studies of infection in patients with inherited immune defects of antibody responses and from patients
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28 139 receiving B cell depleting therapies in whom robust CD8+ T cell responses contributed to increased survival
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30 140 [69-72]. SARS-CoV-2-specific T cell responses are detected to a range of structural (NP, M, ORF3a, spike) and
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32 141 non-structural (ORF7/8, NSP7, NSP13) proteins following SARS-CoV-2 infection [65, 67, 73-76]. Despite these
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34 142 positive correlations the exact role for T cell responses, and which epitopes will be the most protective, remain
35
36 143 unclear. Following natural infection, the memory phase is dominated by more CD4+/helper T cells with
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38 144 follicular helper T cells (Tfh) correlating with humoral immunity [77, 78]. Experience from SARS-CoV-1 and
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40 145 MERS also suggests that T cell immunity against SARS-CoV-2 may be more enduring [67] and reassuringly
41
42 146 largely retained against the highly transmissible Omicron viral variant [79, 80]. Burgeoning evidence also
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44 147 supports a potential role of pre-existing T cell responses in preventing initial infection [81]. Several studies
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46 148 have shown mainly CD4+ T cell responses in up to 50% of samples from blood donors prior to when SARS-
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48 149 CoV-2 appeared in the human population [67, 73, 82-85]. The majority of these T cell responses are to non-
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50 150 spike peptides, including polymerase-specific T cells that were found to expand in abortive SARS-CoV-2
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52 151 infection [81], but some responses to spike were also reported [73]. It has been proposed that this cross
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2 152 reactivity is due to previous infection with common cold coronaviruses, which were circulating in the human
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4 153 population prior to 2019 [86], such as human coronavirus HCoV-229E, HCoV-NL63, HCoV-HKU1 & OC43 [87-
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6 154 90]. Kundu *et al* examined the role of pre-existing cross-reactive T cell responses in protecting SARS-CoV-2
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8 155 naïve household contacts of patients infected with SARS-CoV-2. In this study, fifty-two confirmed exposed
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10 156 contacts were investigated, and T cell responses assessed in both polymerase chain reaction (PCR)-positive
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12 157 (n=26) and PCR-negative (n=26) contacts. The authors found that the initial frequency of human coronaviruses
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14 158 primed cross-reactive T cells, which secrete interleukin-2 (IL-2), are key to protection in contacts who remained
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16 159 PCR-negative [91]. These findings have implications for future vaccine targets, strongly suggesting that the
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18 160 inclusion of non-spike proteins may be essential to increase the breadth of responses, including to novel
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20 161 variants in the future.

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24 162 A limitation of many studies is that analysis of cellular responses has focused on peripheral blood. It is likely
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26 163 that key T cell responses are being underestimated in the lungs and several studies have shown an increase in
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28 164 T cells in bronchoalveolar lavage (BAL) samples from patients with moderate COVID-19 disease compared to
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30 165 patients with severe disease [64, 92, 93]. It is of note that mucosal immune responses are induced during
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32 166 natural infection [94, 95] but there is little evidence to suggest that current vaccines induce mucosal responses
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34 167 [96, 97] without prior SARS-CoV-2 infection [98]. This is an important area which needs further investigation.
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42 170 **Immunological interplay between HIV and SARS-CoV-2**

43 171 **The immunological landscape of HIV infection and implications for vaccine efficacy**

44 172 HIV infection induces profound disruption of both the innate and adaptive immune system (Figure 1). Primary
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46 173 infection induces systemic immune activation and inflammation accompanied by depletion of the T cell
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48 174 compartment, especially in the gut [99, 100]. If left untreated, ongoing viral replication and chronic
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50 175 inflammation leads to the destruction of CD4+ T cells and a persistent expansion of circulating CD8+ T cell
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52 176 numbers. This resulting inversed CD4/CD8 ratio has been associated with frailty and premature ageing of the
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2 177 immune system leading to higher non-AIDS related morbidity and mortality rates [10, 101-104]. There is an
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4 178 associated reduction in T cell proliferative capacity and cytotoxic potential, which eventually leads to
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6 179 exhaustion [105]. Altered innate immune cell function, such as dysregulation of dendritic cells (DCs), and
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8 180 aberrant responses may also contribute to chronic immune activation and exhaustion [106]. B-cells also
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10 181 develop features of exhaustion relatively early during HIV infection [107]. Abnormal polyclonal activation and
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12 182 poor effector function results in a lack of specific antibody responses, which has been well described [108,
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14 183 109]. The introduction of ART leads to viral suppression, improved CD4+ T cell counts, and partially restored
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16 184 proportions of B-cell subpopulations [107, 110]. The earlier ART is started, the lower the levels of immune
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18 185 activation and inflammation [111], but despite treatment, chronic activation persists and antigen-specific B
19
20 186 and T cell responses, including Tfh cell function, are still impaired [112]. PLWH, despite effective virological
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22 187 suppression, continue to have higher levels of inflammatory mediators, such as IL-6, TNF- α , sCD163, sCD14
23
24 188 and CRP in peripheral blood linked to adverse clinical outcomes [113, 114]. As a result, PLWH are 25 times
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26 189 more likely to suffer from pneumonia and other respiratory diseases, some cancers, and infections, such as
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28 190 influenza and tuberculosis, than HIV negative individuals [115-119]. This raised concerns early in the pandemic
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30 191 that PLWH had a higher risk of infection or a more severe disease course if infected with SARS-CoV-2, despite
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32 192 many PLWH receiving ART, as with other respiratory diseases [120]. Indeed, a more severe disease outcome
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34 193 and increased risk of death has been seen in PLWH, especially when viraemia is not well-controlled or CD4+ T
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36 194 cell count has not been reconstituted sufficiently [20].
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44 196 These immunological changes and persistent immune dysfunction in PLWH also have implications for
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46 197 vaccination success (Figure 1). PLWH have lower responses to several vaccines including influenza [121, 122],
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48 198 tetanus, diphtheria [123], yellow fever [124] and poliomyelitis [125]. Vaccine responses are better where the
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50 199 CD4+ T cell count has been reconstituted following the commencement of ART [121]. In addition, the total
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52 200 duration of seroprotection is shorter than in otherwise healthy persons for most licensed vaccines [26]. As
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54 201 treatment options have improved, the life expectancy for PLWH have increased. Additional health concerns
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1
2 202 such as obesity, hypertension and cardiovascular disease, which contribute further to chronic inflammation
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4 203 and reduce vaccine efficacy, have increased [126]. This mirrors the general trajectory of these conditions in
5
6 204 the population. Furthermore, ageing is independently associated with senescence of both the innate and
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8 205 adaptive immune systems [127], leading to innate immune cell dysfunction and a reduction in the humoral
9
10 206 and cellular responses to several viral and bacterial vaccinations [126]. This age-related loss of immune
11
12 207 function, which may be accelerated in PLWH, in addition to changes to the T cell compartment and reduction
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14 208 in the naïve T cell pool, could decrease immune responses to vaccination [112, 121, 122, 128, 129]. Along
15
16 209 these lines, the immunogenicity to mRNA [130, 131] and Adenovirus vector [132] SARS-CoV-2 vaccines have
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18 210 been shown to be diminished in healthy subjects over the age of 55 years compared to those under 55 [133,
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20 211 134]. Elderly individuals also show evidence of reduction in somatic hypermutation of class-switched cells and
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22 212 lower cellular responses following BNT162b2 vaccination [135]. Interestingly, responses were improved
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24 213 following the administration of booster doses [130-132], highlighting that an ageing immune system is a key
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26 214 consideration for the efficacy of currently licensed SARS-CoV-2 vaccines, warranting specific measures to boost
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28 215 responses, especially considering circulating VOCs.
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35 217 When debating additional factors influencing immune responses to vaccination in PLWH, it is essential to
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37 218 account for the effect of chronic co-infections (e.g., viral Hepatitis B and C). These commonly occur in PLWH
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39 219 and have overtaken other opportunistic infections as the leading cause of death in PLWH [129] and have been
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41 220 linked to a reduction in vaccine efficacy [10, 126, 136, 137]. Co-infection with cytomegalovirus (CMV) is
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43 221 particularly prevalent in PLWH [138]. This contributes to a persistent immune activation state, described
44
45 222 herein, through modification of the gut microbiota and microbial translocation, directing responses against
46
47 223 itself, and by induction of immune senescence. These factors lead to a decrease in vaccine responses. SARS-
48
49 224 CoV-2 vaccination success is also improved when patient CD4+ T cell counts are above 350 cells/ μ L, prior to
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51 225 immunization (Table 1). Similarly, in the case of Hepatitis B vaccination, the CD4/CD8 ratio has proved an
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53 226 accurate predictor of vaccine success [139]. This is not surprising given that a low CD4/CD8 ratio is a marker of
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1
2 227 immune senescence [140] and therefore may be an important stratification tool to consider as part of
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4 228 vaccination policies for PLWH.
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229 Immune responses to natural SARS-CoV-2 infection in PLWH

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9 230 Insights from studies examining the quantity and quality of immune responses in people who have recovered
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11 231 from natural infection with SARS-CoV-2 can help inform the optimisation of vaccines. Arguably any underlying
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13 232 differences in cellular compositions (both innate and adaptive immune phenotypes), in addition to
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15 233 uncontrolled viraemia and persistent inflammation in PLWH, could lead to poorly co-ordinated immune
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17 234 responses, affecting the trajectory of COVID-19 disease (Figure 1). Dysregulated immune cell co-ordination has
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19
20 235 been shown to attenuate protective immune responses in elderly individuals [61], which could be highly
21
22 236 pertinent in PLWH with additional co-morbidities. To date there are limited data on natural immunity following
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24 237 SARS-CoV-2 infection in PLWH from studies which are conducted in high-income countries, and in populations
25
26 238 largely controlled on ART.

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29 239 Given that antibody responses are thought to be an important immune correlate of protection, SARS-CoV-2
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31 240 IgG levels and neutralising antibody activity have been compared in PLWH and HIV negative individuals
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33 241 following natural infection. In a matched case-control observational study involving 955 PLWH and 1062
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35 242 people without HIV, the SARS-CoV-2 IgG seroprevalence was 3.7% and 7.4% respectively. Notably, lower anti-
36
37 243 RBD IgG and pseudovirus neutralising antibody titres, with similar avidity, were observed in the HIV positive
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39 244 group compared with HIV negative individuals with evidence of past infection [141]. This is in contrast to
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41
42 245 smaller studies that did not show any difference in IgG concentrations or neutralisation potency against SARS-
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44 246 CoV-2 infection in PLWH. Of note, the latter studies included patients who had well-controlled HIV on ART,
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46 247 which may have been a confounding factor [142-144]. Indeed, a correlation between higher CD4+ T cell count
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49 248 and higher neutralisation titres in COVID-19 infection has been described in PLWH [145-148]. At present, an
50
51 249 in-depth assessment of B-cell specific memory responses is lacking in the setting of HIV infection.

52
53 250 The role of T cells in SARS-CoV-2/HIV co-infection is still being deciphered. Unpicking the increased risk due to
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55 251 HIV infection rather than the high risk of co-morbidities is challenging. It remains unclear whether HIV-

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2 252 associated immune dysfunction and inflammation is linked to severe COVID-19 disease outcomes [149, 150]
3
4 253 or whether paradoxically a low CD4+ T cell count ameliorate disease severity [134]. A recent study by Sharov
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6 254 *et al.* compared the T cell profile and cytokine dynamics of patients with COVID-19 disease with and without
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8 255 HIV infection [146]. Of the 367 patients with HIV, 171 were not on ART due to medication shortages during the
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10 256 pandemic. While a similar T cell response was seen in HIV seronegative and HIV positive patients receiving
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12 257 ART, patients with uncontrolled HIV infection had an attenuated T cell response. A decline in CD4/CD8 ratio
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14 258 was associated with a poorer disease outcome. As expected, T cells displayed a higher rate of T cell exhaustion
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16 259 in HIV infection, characterised by an increased expression of PD-1 and TIM-3. This was more pronounced in
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18 260 the presence of HIV viraemia, suggesting a synergistic effect of HIV/SARS-CoV-2 co-infection on T cell
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20 261 dysfunction. PLWH in the absence of ART had decreased serum concentrations of IL-2, TNF- α and IFN- γ and
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22 262 higher levels of the immunosuppressive cytokines IL-10 and TGF- β [146]. Findings by Alrubayyi and colleagues
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24 263 showed that PLWH, with well-controlled HIV, in the convalescent phase of predominately mild COVID-19
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26 264 disease, showed equivalent magnitude of SARS-CoV-2 specific T cell responses compared to HIV negative
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28 265 individuals, targeting both structural and non-structural proteins [133]. SARS-Cov-2 specific T cell responses
29
30 266 were dominated by CD4+ T cells. Remarkably, a positive association was noted between naïve CD4+ T cells,
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32 267 the CD4:CD8 ratio and the magnitude of T cell responses against SARS-CoV-2 in PLWH. These findings suggest
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34 268 that in addition to viraemic HIV infection, inadequate reconstitution of the T cell compartment and fewer pre-
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36 269 existing naïve T cells could hinder the development of memory responses to SARS-CoV-2 infection [142].
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38 270 Whether dysregulated priming, impairment of Tfh cells and other biological factors not captured in the
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40 271 published studies contribute to poorly co-ordinated humoral and cellular responses remains to be determined.
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42 272 Remarkably, an increasing number of cases of prolonged COVID-19 infection and/or asymptomatic shedding
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44 273 are being reported in people with advanced immunosuppression [151-153]. Whilst this underscores the
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46 274 importance of a functional immune response in viral clearance [65] it also has implications for SARS-CoV-2 viral
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48 275 evolution. Prolonged infections provide an opportunity for SARS-CoV-2 to evolve a multitude of mutations, as
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50 276 SARS-CoV-2 mutates at a relatively slow rate compared to other RNA viruses, due the presence of a proof
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2 277 reading mechanism [154]. This was recently demonstrated in an HIV positive woman with unsuppressed HIV
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4 278 and persistent shedding of SARS-CoV-2 for 210 days, during which time SARS-CoV-2 accumulated 30 mutations,
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6 279 some associated with vaccine escape [153, 155].
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9 280 Additionally, evidence is emerging that PLWH may be more likely to develop post-acute sequelae or “long-
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11 281 covid” [156, 157] However, an accurate picture of the burden of long-covid in this population remains to be
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13 282 determined, including whether immune cell perturbations described in HIV infection may predispose to long-
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15 283 standing symptoms.
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17 284 Despite the significant gaps in our knowledge and lack of granular data on immune responses in PLWH with
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19 285 different levels of HIV-related immunosuppression, these findings highlight the need for early access to
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21 286 effective ART and support vaccine prioritisation in PLWH. Larger studies are needed, particularly for sub-
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23 287 populations of PLWH (e.g., those with low CD4+ T cell counts) or those with identified high risk co-morbidities,
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25 288 especially in high HIV burden areas to help inform vaccine recommendations and therapeutics.
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290 SARS-Cov2 Vaccine Trial Data in PLWH

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35 291 The Spike glycoprotein has been an excellent target for SARS-CoV-2 vaccines, which have been developed at
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37 292 an impressive speed, as a result of a collective effort by regulatory agencies, pharmaceutical companies and
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39 293 the scientific community [158]. Currently licensed vaccines include mRNA vaccines (mRNA-1273 and
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41 294 BNT162b2) [46, 48], non-replicating adenoviral vectors (ChAdOx1 nCoV-19 and Ad26.COV2.S), viral proteins
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43 295 with an adjuvant (NVX-CoV2373) [159] and inactivated SARS-CoV-2 virus (BIBP-CorV) [160]. Several large phase
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45 296 2/3 trials of SARS-CoV-2 vaccines have shown them to be safe and highly effective in the general population.
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48 297 However, after two doses effectiveness reaches 65-90% against infection or mild disease, and 90-100% against
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50 298 severe disease prior to the emergence of VOCs [46-48, 161]. Although individuals with stable treated HIV
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52 299 infection were not excluded in some from the larger phase 2/3 trials, they made up a small proportion of
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54 300 participants (approximately 196 for the BNT162b2 mRNA vaccine [48], 176 for the mRNA-1273 mRNA vaccine
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56 301 [46] and 107 PLWH for the ChAdOx1 viral vectored vaccine [47]). Not all the data on PLWH has been presented
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2 302 to date and the small numbers make interpretation on vaccine efficacy difficult. The Ad26.COVS trial has
3
4 303 included by far the largest number of PLWH (467 people well-controlled with a CD4+ T cell count >300 received
5
6 304 a single dose and 498 received a placebo). Two people from the vaccine group and four people from the
7
8 305 placebo group developed moderate to severe COVID-19 disease 28 days post vaccination [162]. It may be that
9
10 306 certain vaccine platforms will not be as effective in PLWH or other immunocompromised individuals. Some
11
12 307 concerns about the efficacy of NVX-CoV2373 sub-unit vaccine in PLWH have been raised. In one of the pivotal
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14 308 phase 2a–b trials conducted in South Africa, overall vaccine efficacy dropped from 60.1% to 49.4% when PLWH
15
16 309 were included. It is of note that this study was not powered to specifically describe efficacy in the participants
17
18 310 with HIV but highlighted the need to specifically assess vaccine efficacy in PLWH [159]. Importantly in this
19
20 311 study, 92.7% of sequence cases of SARS-CoV-2 infection accounted for the B.1.351 variant [159]. When
21
22 312 assessing vaccine efficacy in PLWH, in addition to numbers included, it is important to consider definitions of
23
24 313 efficacy and the epidemiological setting. To date, there are no head-to-head comparisons between vaccines
25
26 314 and, as such, whether a certain vaccine platform is more effective in PLWH remains unknown. Future planned
27
28 315 studies are planned to address remaining concerns/uncertainties for COVID-19 vaccines in PLWH
29
30 316 (NCT04533399; NCT04754698). The main findings of COVID-19 vaccine studies in PLWH are summarised in
31
32 317 Table 1.

318 **Vaccine Safety for PLWH**

319 Whilst safety concerns surrounding the licensed SAR-CoV-2 vaccines have been publicly voiced and in turn
320 addressed by the scientific community, there have been no additional concerns regarding safety of SARS-CoV-2
321 vaccinations in PLWH. The most commonly reported side effects include mild local and systemic reactions, and
322 these have been shown to occur equally in PLWH and the general population [163]. There have been some
323 reports of HIV viral blips following mRNA vaccinations. Levy *et al* highlighted 3 cases who have low level
324 viraemia (<100 copies/ml) and a separate case report described a patient who had a viral load of 1760
325 copies/ml [164, 165] following vaccination. All of these cases had nadir CD4+ T cell counts of <200 cells/mL

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1
2 326 and/or very high viral loads at diagnosis. However, Levy and colleagues concluded that SARS-CoV-2 vaccination
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4 327 is safe and efficacious in PLWH, with stable CD4+ T cell counts and well-controlled viraemia. Viral blips have
5
6 328 been noted with other vaccines, including influenza and hepatitis B, typically 7-14 days following vaccination
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8
9 329 [166] but these are transient and may be attributed to a reactivation of the latent reservoir. The interplay of
10
11 330 SARS-CoV-2 vaccines, the immune system, and latent HIV infection is yet to be thoroughly understood.
12
13 331 However, these observations suggest that viral load monitoring post-vaccination may be useful in future
14
15 332 studies, particularly for those with low CD4+ T cell counts. It should be highlighted that the benefit of receiving
16
17 333 vaccination outweighs the risk.; this key finding is highlighted by the vaccine trials summarised in Table 1.
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335 SARS-CoV-2 vaccine immunogenicity in PLWH**336 mRNA vaccines**

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30 337 Immune responses in PLWH following vaccination with mRNA-based vaccines have been studied more
31
32 338 extensively. Two prospective cohort trials [167, 168] and one non-interventional study [169] which compared
33
34 339 humoral responses in PLWH and people without HIV found that while the responses to the priming dose of
35
36 340 mRNA vaccine were lower in PLWH, following the second dose humoral responses these were comparable to
37
38 341 that observed in HIV negative participants. Several small studies have demonstrated excellent seroconversion
39
40 342 rates (as measured by detection of spike-RBD specific IgG) with positive responses in 97-98% of PLWH following
41
42 343 two vaccines. Notably, these findings were observed in the context of well-controlled HIV [164, 170, 171] with
43
44 344 comparable neutralising antibody titres to HIV negative people [172]. The requirement for at least 2 doses of
45
46 345 mRNA vaccines was further highlighted by Woldemeskel *et al*, demonstrating equivalent SARS-CoV-2 spike
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48 346 binding antibody titres and cellular responses (assessed by T cell IFN- γ production) irrespective of HIV status.
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51 347 Additionally, there was no significant difference in BNT162b2-elicited SARS-CoV-2 binding antibody levels to
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1
2 348 the Beta, Alpha and Gamma variants. Despite this, the numbers in this study are small and its findings need to
3
4 349 be interpreted with caution [173, 174].
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6
7 350 mRNA vaccine immunogenicity is less well-described in PLWH with ongoing immunosuppression and viraemia,
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9 351 who are a particularly vulnerable group that is poorly represented in vaccine trials. In a single case report, lack
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11 352 of seroconversion and no detectable cellular responses were observed following two doses of BNT162b2 in a
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13 353 patient who was vaccinated prior to ART initiation (CD4+ T cell count of 20 cells/ μ L) [175]. This is consistent
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15 354 with lower seroconversion rates in people with underlying malignancies and transplant recipients [176].
16
17 355 Emerging evidence presented at recent international meetings, indicates that lower CD4+ T cell counts <250
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19 356 cells/ μ L, viraemia and/or previous AIDS associate with significantly weaker spike antibody responses, weaker
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21 357 cellular responses and a higher risk of waning neutralising activity after a median of 5 months in PLWH. This
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23 358 identifies them as more vulnerable to reduced vaccine efficacy [175, 177-180]. PLWH with a CD4+ T cell count
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25 359 <250 cells/ μ L were found to have a reduced neutralising ability against the Beta and the Delta variant. No data
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27 360 against Omicron are currently available [180]. As expected, prior SARS-CoV-2 infection predicted higher spike
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29 361 antibodies, as observed for the general population [179]. In an Italian study, a third dose mRNA booster of
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31 362 either BNT162B2 or mRNA-1273 >28 days following a complete mRNA vaccination course was found to
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33 363 strongly boost humoral responses in PLWH with advanced disease (CD4+ T cell count <200 cells/ μ L and/or
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35 364 previous AIDS). This was irrespective of the patients' CD4+ T cell count at the time of boosting and supports
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37 365 the use of an additional vaccine dose in this patient group [181].
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44 366 **Adenovirus Vectored vaccines**

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47 367 The Adenovirus vector-based vaccine ChAdOx1 nCoV-19 has also been shown to induce equivalent humoral
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49 368 responses in PLWH and HIV negative volunteers. Three published studies compared spike-specific IgG
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51 369 responses and neutralising antibody profiles of HIV negative individuals to PLWH with well-controlled HIV and
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53 370 CD4+ T cell counts >350cells/ μ L. No significant differences were found based on HIV status [182-184].
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55 371 Encouragingly, Madhi *et al* demonstrated that 50% of PLWH had cross-reactive binding antibodies to the Beta
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2 372 variant and wild-type[182]. High responders retained this neutralisation capacity against the Beta variant [182-
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4 373 184]. Additionally, T cell responses, determined by ELISpot were comparable to the HIV negative group [182].
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6 374 Data on the durability of these responses have been recently published showing no significant differences in
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8 375 ChadOx1 nCov19 vaccine-mediated responses, according to HIV status, in 54 PLWH CD4+ T cells >350 cells/ μ L
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10 376 and 50 HIV negative age and sex matched controls. Waning but detectable humoral and T cell immune
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12 377 responses against the wild type and VOCs (Alpha, Beta, Gamma and Delta) were observed 6 months after
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14 378 vaccination [183, 185]. Interestingly in this study, prior exposure to circulating β coronaviruses (HKU1 and
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16 379 OC43) was associated with detectable proliferative SARS-CoV-2 T cell responses at baseline, which were
17
18 380 further augmented post-vaccination. This suggests that pre-existing cross-reactive responses could modulate
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20 381 post vaccine responses in PLWH[185].

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22 382 Khan *et al*, reported similar neutralisation responses in PLWH and HIV negative individuals who had been
23
24 383 vaccinated with a different adenovirus-based vaccine (Ad26.COVS.2.S) and subsequently became infected with
25
26 384 the Delta variant [147]. Where as PLWH had previously been infected with SARS-CoV-2 and then vaccinated, a
27
28 385 9-fold higher Delta variant neutralisation was seen compared to the vaccinated only group, indicating that
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30 386 vaccination boosted the neutralisation response reflecting the same phenomena in the general population
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32 387 [147, 172, 182].

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34 388 How these data extrapolate to PLWH with lower CD4+ T cell counts and/or ongoing viraemia is not known and
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36 389 additional research is required to address the immunogenicity and durability of adenovirus vectored vaccines
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38 390 in this sub-group of PLWH.

391 Heterogenous vaccination schedules and breakthrough infection studies

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40 392 Optimising the immunogenicity of vaccines is critical to either stimulate waning immunity or to increase the
41
42 393 breadth of immunity. This is either as part of a primary course or against SARS-CoV-2 protein lineage variants,
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44 394 where reduced efficacy has been reported. Data in HIV infection are scarce regarding the optimal vaccination
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46 395 schedule, including the time interval between prime and boost. In the UK a third dose is given as part of the
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2 396 primary immunisation course in advanced HIV infection (at least eight weeks after the last dose) and
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4 397 subsequent booster doses are recommended after the last vaccine dose for all PLWH. In individuals who
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6 398 completed the ChAdOx1 nCoV-19 vaccine schedule, an mRNA booster vaccination is preferentially advised.
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8 399 Thus far, heterogenous vaccination approaches have shown superior immunogenicity outcomes, quantified by
9
10 400 both humoral and cellular responses to the wild type virus and its variants [186]. Both animal studies and
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12 401 emerging evidence in humans, suggest that adenovirus-vectored prime followed by an mRNA boost, at an
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14 402 interval of 6-12 weeks, provides enhanced humoral and cellular responses compared to homologous
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16 403 vaccination [186-191]. In a non-interventional retrospective study, including 665 PLWH in Germany, Noe *et al*
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18 404 described the anti-SARS-CoV-2 antibody response following standard vaccination (heterologous and
19
20 405 homologous) schedules [21]. They found that mRNA vaccination schedules, being female, and having a higher
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22 406 CD4+ T cell count was associated with a higher concentration of antibodies in PLWH. There was a markedly
23
24 407 lower response in PLWH with a CD4+ T cell count < 200 cells/ μ L, however, as with other studies, the numbers
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26 408 were small. Further studies would be required to confirm if these reduced responses do result in a higher risk
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28 409 of infection and more severe disease. Questions on the optimisation of current vaccine schedules and
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30 410 flexibility in using different COVID-19 vaccines were addressed in the Com-CoV2 study in HIV negative adults
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32 411 aged 50 years and over. These adults were immunised with either: a single dose of ChAdOx1 nCoV-19 or
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34 412 BNT162B2, or heterologous dosing with mRNA-1273 but not NVX-CoV2373. This resulted in increased
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36 413 reactogenicity compared with homologous schedules [192]. Further work is required to address the effects of
37
38 414 this mix and match approach prospectively in PLWH with differing levels of immunosuppression and/or natural
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40 415 exposure to SARS-CoV-2 and circulating variants as the epidemic evolves. It is likely that these approaches will
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42 416 add resilience to circulating variants by inducing stimulation of complementary immune pathways, leading to
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44 417 more effective and durable B cell and T cell responses.
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52 418 To date, few studies have analysed the rates of breakthrough infections in PLWH. Data from Israel has
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54 419 estimated that approximately 40% of breakthrough infections occur in immunocompromised individuals [176].
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56 420 Two large longitudinal cohorts in the US have estimated a similar number of breakthrough SARS-CoV-2
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2 421 infections in vaccinated PLWH compared to people without HIV which included 8,536 [193] and 31,840 PWH
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4 422 [194]. Both studies found a 33-41% higher risk of breakthrough infection in PLWH, which persisted after
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6 423 regression analysis for covariates such as age, race/ethnicity, and sex at birth. Conversely, booster recipients
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8 424 had a reduced risk of infection compared to those who were not boosted, as well as a reduced risk of severe
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10 425 COVID-19 disease outcomes. This indicates that boosters are important tools of protection for PLWH.
11
12 426 Interestingly, in contrast to vaccination studies described herein, Coburn and colleagues did not find any
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14 427 correlation between CD4+ T cell count and/or HIV viraemia to be associated with breakthrough risk [194].
15
16 428 However, it should be noted that data on breakthrough infections is limited by diagnostic testing practices and
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18 429 access to healthcare. As with many of the studies included in this review, the duration of ART and the level of
19
20 430 suppression required is not consistent between studies and therefore, it is more difficult to untangle the
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22 431 specific effects of these variables and how they may impact vaccine responses.
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27 432 As for the general population it is expected that additional vaccine doses will offer some degree of protection
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29 433 against omicron and severe disease requiring hospitalisation. Early data from Israel in people aged 60 or older
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31 434 showed that a fourth dose mRNA vaccine against omicron reduces the risk of infection and disease severity.
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33 435 At present HIV-specific data following a fourth (and/or additional vaccine doses) are lacking[195].
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437 Limitations of SARS-Cov-2 Vaccines studies in PLWH

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44 438 There is currently a lack of standardised assays for determining vaccine efficacy and correlation of protection
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46 439 for humoral or cellular immune responses. The gold standard for vaccine efficacy is neutralising antibody
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48 440 responses but there are a number of different assays utilised in studies. These include live-virus neutralisation
49
50 441 [196], pseudotype virus neutralisation [196, 197] and surrogate neutralisation assays [198]. A consensus on
51
52 442 the ideal neutralisation assay has not yet been reached as pseudovirus-based assays are not routinely utilised
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54 443 in clinical care. Live-virus neutralisation assays are labour intensive and can only be performed by specialist
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2 444 high-containment laboratories with highly trained staff [199]. To address this, several groups have attempted
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4 445 to produce standards, which could be used for comparison of data between labs [35, 200]. This is critical to
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6 446 fully comprehend vaccine responses in PLWH as aggregation of data collected from diverse neutralisation, RBD
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8 447 and ELISA assays, and clinical trial designs is required to make statistically significant conclusions. Moreover,
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10 448 the selection of appropriate assays is complicated by the potential for false positives due to interference with
11
12 449 anti-retrovirals (e.g. reverse transcriptase and integrase inhibitors), especially in cell-based assays and
13
14 450 lentiviral-vector pseudotype virus assays [201]. Additionally, the inclusion of some patients with prior SARS-
15
16 451 CoV-2 infection makes interpretation of vaccine response more complex, especially as studies in HIV negative
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18 452 people have shown that previous infection with SARS-CoV-2 enhances T cell and antibody responses post
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20 453 vaccination [131, 202, 203].
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25 454 There are very few studies which focus on the cellular response to SARS-CoV-2 vaccination in PLWH, which may
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27 455 be in part due to technical difficulties in carrying out cellular-based assays. The assumption that the degree of
28
29 456 humoral response is paralleled by the cellular immune response may not hold true for PLWH given the distinct
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31 457 T cell dysregulation that occurs. This might be particularly relevant for PLWH with depleted of CD4+ T cells,
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33 458 who appear to be at higher risk of severe COVID-19, and reduced responsiveness to vaccine. As with
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35 459 neutralisation data, the numbers of PLWH included in published studies are small. Hence, they are unable to
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37 460 adequately adjust for many confounding variables that may affect vaccine responses. In addition, data for
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39 461 SARS-CoV-2 vaccine response for PLWH over the age of 55 is scarce and the combined effect of ageing, chronic
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41 462 illness and HIV infection on vaccines responses is yet to be fully understood, and may in part, account for the
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43 463 findings of higher risk breakthrough infections described in PLWH.
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49 464 **Concluding remarks and remaining challenges**

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51 465 PLWH have been dealing with a great deal of uncertainty throughout the pandemic, particularly as evidence
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53 466 regarding risk of disease severity has been conflicting, and data on vaccine efficacy remain limited. Studies of
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55 467 seroconversion rates, and neutralisation titres post SARS-CoV-2 vaccination in PLWH, are reassuring for those
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1
2 468 who have stable HIV on ART and preserved immune function. These findings further highlight the critical role
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4 469 of CD4+ T cells as facilitators of effective humoral responses and offer insights into the complementary role of
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6 470 T cell specific responses in mediating protection, which may be hindered in people with incomplete immune
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8 471 reconstitution and/or a diminished repertoire of naïve T cells. However, as there is not a consensus on what
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10 472 constitutes protective immunity, it is hard to define protective efficacy in immunocompromised individuals. In
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12 473 particular further work is required to disentangle the importance of T cell immunity in vaccine-mediated
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14 474 protection against SARS-CoV-2 and circulating variants. What is becoming apparent is that PLWH should follow
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16 475 current recommended vaccination schedules and boosters as they become available. This is given that SARS-
17
18 476 CoV-2 vaccination is safe and efficacious; overall vaccine effectiveness was 65% (95%CI: 56%-72%, P <0.001)
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20 477 among vaccinated compared to unvaccinated PLWH [163]. However, these data need to be continuously
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22 478 evaluated in the context of the evolving pandemic, prevalence of circulating variants, different vaccination
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24 479 schedules and number of doses.

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28 480 Male adults living in Europe, the United States, and South Africa are the most represented participants to date,
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30 481 which poorly reflects the global prevalence of PLWH. Although the primary aim is to start PLWH on ART
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32 482 immediately, this is not always possible in resource-limited settings. The pandemic has further highlighted
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34 483 disparities in access to ART and global disparities in vaccine coverage, which may leave PLWH potentially
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36 484 vulnerable [146, 204]. There is evidence of worse COVID-19 disease outcomes in patients with coinfections,
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38 485 such as *Mycobacterium tuberculosis* (TB) [16, 17]. The intersecting SARS-CoV-2, HIV, and TB epidemics pose
39
40 486 additional concerns, particularly as T cell immunity and SARS-CoV-2-specific CD4+ T cells are reduced and
41
42 487 display lower polyfunctional capacity in the setting of co-infection [148].

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44 488 A potential confounding factor in the evaluation of vaccine efficacy in PLWH is the use of ART as some, i.e.
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46 489 lopinavir-ritonavir, have anti-coronavirus activity *in vitro* [205]. Although a role of ART in preventing
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48 490 complications of COVID-19 has been postulated, it is unlikely that the plasma concentrations of ART are enough
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50 491 to inhibit SARS-CoV-2 replication [206]. Lopinavir-ritonavir has not been shown to reduce inpatient mortality
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52 492 or hospitalisation length in patients with COVID-19 and is not currently a recommended therapy [207].
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2 493 Importantly, it is also becoming increasingly apparent that PLWH represent a diverse population in terms of
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4 494 their immune phenotype and levels of immunosuppression. Specific subgroups could therefore benefit from
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6 495 distinct immunisation strategies, such as an adapted vaccine schedule and additional doses to increase
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8 496 protection against severe disease. For instance, altered dose regimens, repeat vaccine series or use of
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10 497 adjuvants may be needed as an additional strategy to improve immunological responses in PLWH with
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12 498 evidence of immunodeficiency or additional co-morbidities, as shown for other vaccines [208, 209].
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14 499 Assessment of total CD4+ T cell, CD4:CD8 ratios and levels of viraemia should be considered in determining
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16 500 vaccine scheduling and efficacy, with the caveat that it will not capture the full immune profile. Although
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18 501 correlates of protection are currently unknown, spike-antibody ELISA assays are accessible assays and have
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20 502 been shown to correlate with neutralising antibody responses [29] with the caveat that these responses are
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22 503 reduced against circulating VOCs [210] [211]. Post-vaccination testing for spike antibody could be considered,
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24 504 however, to identify subpopulations of immunocompromised people who may not mount an immune
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26 505 response and therefore require additional protection. Future research should aim to assess the magnitude and
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28 506 the durability of SARS-CoV-2 vaccine-induced antibody and T cell responses in PLWH with particular focus on
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30 507 those with uncontrolled viral infection and/or who have low CD4+ T cell counts to inform the best strategy for
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32 508 boosting. Greater attention needs to be paid to the combined effect of ageing, co-morbidities, and HIV
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34 509 infection as part of the research agenda. Finally, a consensus of assays used for assessment of vaccine
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36 510 responses and a threshold of protection for humoral and cellular responses would greatly benefit assessment
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38 511 of required responses in PLWH.
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513 Data Availability

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515 All data are contained within the manuscript.

516

517 Conflict of Interest Statement

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2 518 *The authors declare that the research was conducted in the absence of any commercial or financial*
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4 519 *relationships that could be construed as a potential conflict of interest.*

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6
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8
9
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Vaccine, dose, country and author	Trial Design,	Participant characteristics	CD4+ T cell Count/HIV control (PLWH)	Prior SARS-CoV-2 infection	Immunological readout	Impact for PLWH
ChAdOx1 Two doses UK Frater <i>et al</i> , [183]	Phase 2/3	54 PLWH (all male), Median age 42.5 years, (IQR 37.5-49.8) 50 HIV negative (24 female, 25 male), Median age 38.5 years, (IQR 29.2 – 45.0)	All PLWH on ART for at least 3 months Median CD4+ T-cell count 694, (IQR 574-860)	Not part of study criteria	IgG spike binding antibody (ELISA) Live virus Neutralisation ELISpot T-cell proliferation	Replication deficient adenoviral vector vaccine induces response in PLWH Comparable cellular and humoral responses (magnitude or persistence of response) to HIV negative participants No correlation between the magnitude of the anti-spike IgG response at day 56 and CD4+ T cell count (p=0.93) or age (p=0.48)
ChAdOx1 Two doses South Africa Madhi <i>et al</i> , [182]	Randomised, double-blind, placebo-controlled, phase 1B/2A trial	103 PLWH 51 Placebo (11 male, 40 female), Median age 41 years (IQR 33-46) 52 Vaccinated (16 male, 36 female), Median age 37 years (IQR 36-46) 58 HIV negative 31 Placebo (19 male, 10 female),	All PLWH on ART for at least 3 months Plasma viral load >100 copies/ml Median CD4+ T cell count 695, (IQR 512–929)	6 HIV negative participants tested seropositive for SARS-CoV-2 at baseline 8 PLWH tested seropositive for SARS-CoV-2 at baseline	Binding antibody (ELISA) Neutralisation	Replication deficient adenoviral vector vaccine induces response in PWLH Participants testing seropositive at baseline had higher levels of spike antibodies and neutralizing titres regardless of HIV status Antibody and neutralisation titres increased in all participants following second dose of vaccine

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		Median age 31 years, (IQR 26-42)				
		29 vaccinated (17 male, 12 female), Median age 34 years (range 23-41)				
Ad26.CoV2. S Single dose South Africa Khan <i>et al</i> , [147]	Participants from the SISONKE South African clinical	26 PLWH (i) Infected unvaccinated n=34 (7 male & 27 female), Median age 41 years (ii) infected vaccinated n=18 All female, Median age 47 years (iii) vaccinated only n=8, (1 male & 7 female) 73 HIV negative between 3 groups	All PLWH receiving ART 10 viraemic SARS-CoV-2 infected and unvaccinated (HIV viral load 1224-30160 copies/mL), Median CD4+ T cell count 581 1 viraemic SARS-CoV-2 vaccinated (HIV viral load 3219 copies/mL), Median CD4+ T cell count 852 Non-viraemic vaccinated, participants, Median CD4+ T-cell count 735	Actively enrolled unvaccinated & vaccinated participants with prior SARS-COV-2 infection	Neutralisation Vs Delta variant only	Participants with well controlled HIV had comparable neutralisation of delta variant, regardless of prior SARS-CoV-2 infection Weakest responses seen in unvaccinated PLWH with prior SAR-CoV-2 infection, particularly in those with HIV viraemia
BNT162b2 (mRNA)	Pilot study	12 PLWH (5 male & 7 female), Median	All PLWH receiving ART	No evidence of prior SARS-	CD4 and CD8 ELISpot	mRNA vaccine induces antibody responses in

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15	Two doses USA Woldemeskel <i>et al</i> , [173, 174]	age 52 years, (IQR 25-59) 17 HIV negative (7 female & 10 male), Median age 41 years, (IQR 24-59)	3 participants had HIV viral load >20 copies/mL Median CD4+ T cell count 913	CoV-2 infection (determined by lack of detectable nucleocapsid antibodies)	Anti-spike IgG – ELISA	PLWH Magnitude and breadth of antibody & T cell responses not significantly different from HIV negative participants, which could be CD4+ T cell count dependent
16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34	BNT162b2 (mRNA) Two doses Israel Levy <i>et al</i> , [164]	143 PLWH (131 male & 12 female), Mean age 49.8 years 261 HIV negative (66 male & 195 female), Mean age 55.8 years	All PLWH on ART 95% undetectable HIV viral load Mean CD4+ T cell count at baseline 700 Mean nadir CD4+ T- cell count 345	Not part of study criteria	Binding IgG (RBD)(ELISA) pMN (pseudotype micro- neutralisation)	mRNA vaccine induces antibody responses in PLWH Total IgG responses to RBD lower in immunocompromised controls but neutralizing antibodies at similar level to controls Decrease in CD4+ T cell counts observed after each vaccine dose - may impact PLWH with low/unstable CD4+ T cell counts
35 36 37 38 39 40 41 42 43 44 45 46 47	BNT162b2 (mRNA) Two doses Sweden	90 PLWH (54 male & 36 female), 79% under 65 years 90 controls (29 male & 36 female),	Latest CD4+ T cell count ≤ 300, n= 30 Latest CD4+ T cell count >300, n= 60	Individuals with prior SARS-CoV-2 infection were excluded	Anti-spike IgG (ELISA)	The primary endpoint was seroconversion rate two weeks post second dose 100% of PLWH with CD4+ T cell counts >300 seroconverted following

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Bergman <i>et al</i> [170]		70% under 65 Additional participants with primary immunodeficiency disorders or secondary immunodeficiency disorders (n=90 per group)				vaccination 96% of PLWH with CD4+ T cell counts <300 PLWH were the only secondary immunodeficiency group which did not have a higher likelihood to seroconvert
BNT162b2 (mRNA)Prime and boost data (two doses total) Germany Jedicke <i>et al</i> , [168]	Cohort observational study	PLWH After prime n=88 (75 male & 13 female), Mean age 53.8 years (range 26-86 years) After boost n= 52, (39 male & 13 female), Mean age 60.2 years (range 32-85) HCW (controls) n=41 after prime and boost (13 male & 28 female), Mean age 44 years (range 23-61)	Viral load <50 copies /mL, n= 84 participants after prime and n= 51 participants after boost Viral load of 51-200 copies/mL, n= 4 participants after prime and n=1 participant after boost Mean CD4+ T cell count 716 after prime & 577 after boost Mean nadir CD4+ T-cell count 257 after prime & 199 after boost	Not included in study design	Binding IgG & IgA (ELISA) Inhibition by virus surrogate neutralisation test (c-pass kit)	All PLWH receiving ART mounted a humoral response regardless of nadir CD4+ T cell count, current CD4+ T cell count, CD4:CD8 ratio after full vaccination. Overall levels of anti-RBD antibodies were variable HIV-negative controls produced significantly higher mean anti-RBD antibody concentrations with less variability

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	1 dose of mRNA vaccines: Moderna (PLWH) or Pfizer (Control group) Canada Nault <i>et al</i> , [167]	Cohort observational study 3-4 weeks post vaccination	106 PLWH (90% male), Mean age 43 years (range 21-65) 20 HIV negative HCW (healthcare workers), Mean age 47 years (range 21-59)	CD4+ T cell count <250, n=6 CD4+ T cell count 251 – 500, n=18 CD4+ T cell count >500, n=82 4 participants had detectable HIV viral load	11 participants had seroconverted before vaccination and were excluded from study	Anti-RBD IgG (ELISA)	PLWH with CD4+ T cell counts above 250 had comparable antibody responses to control group Lower CD4+ T cell counts resulted in weak responses Study suggests significant association of age to single dose vaccine response
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	mRNA-1273 Two doses Italy Lombardi <i>et al</i> , [172]	Prospective single centre cohort	71 PLWH (60 male & 11 female), Mean age 47 years 10 HIV negative healthy controls (7 male & 3 female), Mean age 58 years	Median CD4+ T cell count 747 Median HIV viral load <50 copies/mL	9 PLWH and 2 healthy controls had prior infection with SARS-CoV-2 (Confirmed by antibodies to nucleocapsid)	Binding IgG (Roche antibody kit) Neutralising pMN	Vaccination resulted in seroconversion and neutralising antibody responses in PLWH on ART who were virally suppressed with good CD4+ T cell counts. Neutralising antibody and anti-S antibody titres were like those displayed by healthy controls, even when stratified according to the CD4+ T cell count PLWH with prior SARS-CoV-2 infection displayed higher anti-S antibody titres (p=0.0007) and neutralising antibody activity in sera

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						(p=0.0007) than COVID-19-naïve PLWH
2 doses of mRNA vaccines: Moderna (n=9) & Pfizer (n=5) USA Ruddy <i>et al</i> , [171]	Prospective observational cohort	14 PLWH only (13 male & 1 female), Median age 62 years, (IQR 56-70)	All participants on ART for at least 6 months 13 participants had undetectable viral loads. 1 had detectable viral load (not stated) CD4+ T cell counts: <200, n=2, CD4+ T cell count 200-349, n=1, CD4+ T cell count 350-499, n=3 CD4+ T cell count >500, n= 8	Not included in study	Binding IgG antibodies (RBD) (ELISA)	2 doses of mRNA vaccine resulted in high binding antibody titres in PLWH with well controlled HIV on ART, regardless of CD4+ T cell counts
Heterogenous vs homologous vaccine schedule Germany Noe <i>et al</i> , [21]	Non-interventional, retrospective study	665 PLWH mRNA vaccinated n= 590 (492 male, 8 female), Median age 52 years, (IQR 43-59) Heterologous schedule n=29 (25	Whole study: HIV viral load: 93.5% of participants <50 copies/mL Median CD4+ T cell count 708 Median nadir CD4+	Participants with Prior SARS-COV-2 infection were excluded from the study	Obtained from patient files: Anti-SARS-COV-2 antibody levels (ELISA)	Antibody levels achieved by PLWH following vaccination were comparable to general population mRNA containing vaccination schemes (homo or heterogeneous) had highest antibody responses Vector-only vaccination

		male, 4 female), Median age – 56 years, (IQR 48-59) AstraZeneca vaccinated n=31 (all male), Median age 31 years, (IQR 49.5 – 63) Janssen vaccinated n=15 (12 male), Median age 46 years, (IQR 39.5 – 59)	T cell 264			scheme had lower median antibody responses Trend towards better responses in female participants Current CD4+ T cell count significantly associated with antibody responses
Heterologous regimens Canada Brumme <i>et al</i> [169]	Non- interventional trial	100 PLWH (88 male, 12 female), Median age 54 years, (IQR 40-61) 152 HIV negative controls (76 male, 76 female), Median age 47 years, (IQR 35-70)	Median CD4+ T cell count 710	8 PLWH participants included in study 15 HIV negative controls included in study	Anti-nucleocapsid and anti-RBD binding antibodies (Roche) ACE displacement assay Neutralisation (Live virus)	SARS-CoV-2 vaccination induces binding and neutralizing antibody responses in PLWH on ART with CD4 counts in healthy range Older participants and those with other underlying conditions had weaker responses Vaccination with 1 or 2 doses of mRNA vaccination as part of a 2-dose scheme produces higher peak antibody responses than viral vectored vaccination but waned quicker than 2

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						doses of ChAdOx1 Increased interval between vaccine doses resulted in high levels of binding antibodies but not neutralising antibodies
Inactivated whole viral vaccine Prime and boost data (two doses total) China <i>Zou et al</i> [212]	Prospective	46 PLWH (40 male & 6 female), Mean age 38 years 40 HIV negative controls, Mean age 34 years	Median CD4 count 523 CD4+ T cell count <200, n=2 CD4+ T cell count 200-349, n=8 CD4+ T cell count 350-499, n=11 CD4+ T cell count >500, n=25	Not included in study protocol	Neutralisation Binding antibody (IgM & IgG) (ELISA)	Inactivated virus is safe to administer to PLWH PLWH mounted a weaker and delayed humoral response to the inactivated vaccine compared to HIV negative controls
Inactivated whole viral vaccine Two doses China <i>Lv et al</i> [213]	Interventional Study	24 PLWH (12 male & 12 female), Median age 44 years, IQR 39-48.75 – 47. 24 HIV negative controls (15 male & 9 female), Median age 37, IQR 26.25 – 47.25).	CD4+ and CD8+ T-cell count levels were enumerated by flow cytometry after vaccination but numbers prior to vaccination not available	Excluded participants with prior history of exposure or infection with SAR-CoV-2	Neutralisation (Competitive ELISA) Lymphocyte phenotyping (Flow cytometry)	Inactivated whole virus vaccine is safe and capable of inducing neutralising antibody responses in PLWH The magnitude of neutralising antibodies was lower compared to HIV negative participants Lower CD4+ T cell and B cell levels observed following

						vaccination may explain these difference
Inactivated whole viral vaccine	Open-label two-arm non-randomized study	42 HIV (29 male & 13 female), Mean age 42.54 years	All HIV positive participants required to have a CD4+ T cell count of >200 at baseline (mean CD4+ T cell count 659) and 4 weeks after vaccination (mean CD4+ T cell count 476.9)	Participants with prior infection with SAR-CoV-2 were excluded	Neutralisation (surrogate neutralisation assay – Perkin Elmer) RDB binding antibody (ELISA) Lymphocyte phenotyping (Flow cytometry)	Inactivated whole virus vaccine is safe and capable of inducing neutralising antibody responses in PLWH receiving ART and with a CD4+ T cell count of >200CD3+, CD4+, CD8+ T Cell counts of PLWH decreased following vaccination but did not lead to clinical adverse events
Two doses		28 Healthy controls (16 males, 12 females), Mean age 37.79 years				
China						
Feng <i>et al</i>						
[160]						

Table 1 – Summary of SARS-CoV-2 vaccine trial data for people living with HIV (PLWH).

References

1. Dong E, Du H, Gardner L; An interactive web-based dashboard to track COVID-19 in real time. *The Lancet Infectious Diseases* 2020;**20**(5):533-534
2. Ambrosioni J, Blanco JL, Reyes-Urueña JM, *et al.*; Overview of SARS-CoV-2 infection in adults living with HIV. *The Lancet HIV* 2021;**8**(5):e294-e305
3. (UNAIDS) UJPOHA. *UNAIDS DATA 2020*. <https://www.unaids.org/en/resources/documents/2020/unaids-data> (Date last cessed)
4. Li C, Zhu Y, Qi C, *et al.*; Estimating the Prevalence of Asymptomatic COVID-19 Cases and Their Contribution in Transmission - Using Henan Province, China, as an Example. *Frontiers in Medicine* 2021;**8**

- 1
2
3 536 5. Wang D, Hu B, Hu C, *et al.*; Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia
4 537 in Wuhan, China. *JAMA* 2020;**323**(11):1061
- 5 538 6. Huang C, Wang Y, Li X, *et al.*; Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*
6 539 2020;**395**(10223):497-506
- 8 540 7. Ho FK, Petermann-Rocha F, Gray SR, *et al.*; Is older age associated with COVID-19 mortality in the absence of other risk factors?
9 541 General population cohort study of 470,034 participants. *PLOS ONE* 2020;**15**(11):e0241824
- 10
11 542 8. Zheng Z, Peng F, Xu B, *et al.*; Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis.
12 543 *Journal of Infection* 2020;**81**(2):e16-e25
- 13
14 544 9. Richardson S, Hirsch JS, Narasimhan M, *et al.*; Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients
15 545 Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020;**323**(20):2052
- 16
17 546 10. Guaraldi G, Orlando G, Zona S, *et al.*; Premature Age-Related Comorbidities Among HIV-Infected Persons Compared With the
18 547 General Population. *Clinical Infectious Diseases* 2011;**53**(11):1120-1126
- 19 548 11. CDC. *HIV Among People Aged 50 and Over | Age | HIV by Group | HIV/AIDS | CDC.*
20 549 <https://www.cdc.gov/hiv/group/age/olderamericans/index.html>. (Date last cessed)
- 22 550 12. Kim JLK, Kim GE, Kim, S Yang J.W, Li, H Hong, R.A. Ghayda R.A, A. Kronbichler, Koyanagi A, Jacob L, Shin. JI, Smith.L;
23 551 Clinical characteristics and mortality of patients with hematologic malignancies and COVID-19: a systematic review. *Eur Rev Med*
24 552 *Pharmacol Sci* 2020;**24**(22):11926-11933
- 26 553 13. Kates OS, Haydel BM, Florman SS, *et al.*; Coronavirus Disease 2019 in Solid Organ Transplant: A Multicenter Cohort Study.
27 554 *Clinical Infectious Diseases* 2021;**73**(11):e4090-e4099
- 28
29 555 14. Gianfrancesco M, Hyrich KL, Al-Adely S, *et al.*; Characteristics associated with hospitalisation for COVID-19 in people with
30 556 rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Annals of the Rheumatic Diseases*
31 557 2020;**79**(7):859-866
- 32
33 558 15. (WHO) WHO. *WHO-2019-nCoV-Vaccines-SAGE-Prioritization-2022.1*. [https://www.who.int/publications/i/item/who-sage-](https://www.who.int/publications/i/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines)
34 559 [roadmap-for-prioritizing-uses-of-covid-19-vaccines](https://www.who.int/publications/i/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines) (Date last cessed)
- 35
36 560 16. Baskaran V, Lawrence H, Lansbury LE, *et al.*; Co-infection in critically ill patients with COVID-19: an observational cohort study
37 561 from England. *Journal of Medical Microbiology* 2021;**70**(4)
- 38
39 562 17. Boule A, Davies M-A, Hussey H, *et al.*; Risk Factors for Coronavirus Disease 2019 (COVID-19) Death in a Population Cohort
40 563 Study from the Western Cape Province, South Africa. *Clinical Infectious Diseases* 2021;**73**(7):e2005-e2015

- 1
2
3 564 18. Yang X, Sun J, Patel RC, *et al.*; Associations between HIV infection and clinical spectrum of COVID-19: a population level analysis
4 565 based on US National COVID Cohort Collaborative (N3C) data. *The Lancet HIV* 2021;**8**(11):e690-e700
- 5 566 19. Bertagnolio S, Thwin SS, Silva R, *et al.*; Clinical features of, and risk factors for, severe or fatal COVID-19 among people living
6 567 with HIV admitted to hospital: analysis of data from the WHO Global Clinical Platform of COVID-19. *The Lancet HIV* 2022
- 8 568 20. Dandachi D, Geiger G, Montgomery MW, *et al.*; Characteristics, Comorbidities, and Outcomes in a Multicenter Registry of Patients
9 569 With Human Immunodeficiency Virus and Coronavirus Disease 2019. *Clinical Infectious Diseases* 2021;**73**(7):e1964-e1972
- 10
11 570 21. Noe S, Ochana N, Wiese C, *et al.*; Humoral response to SARS-CoV-2 vaccines in people living with HIV. *Infection* 2021
- 12
13 571 22. Hoffmann C, Casado JL, Härter G, *et al.*; Immune deficiency is a risk factor for severe COVID-19 in people living with HIV. *HIV*
14 572 *Medicine* 2021;**22**(5):372-378
- 15 573 23. (BHIVA) BHA. *BHIVA statement on JCVI recommendations for a third COVID-19 vaccine dose.* [https://www.bhiva.org/BHIVA-](https://www.bhiva.org/BHIVA-statement-on-JCVI-recommendations-for-a-third-COVID-19-vaccine-dose)
16 574 [statement-on-JCVI-recommendations-for-a-third-COVID-19-vaccine-dose](https://www.bhiva.org/BHIVA-statement-on-JCVI-recommendations-for-a-third-COVID-19-vaccine-dose) (Date last cessed)
- 18 575 24. (CDC) CfDCap. *COVID-19 Vaccines for Moderately or Severely Immunocompromised People.*
19 576 <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html> (Date last cessed)
- 20
21 577 25. Organisation WH. *WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines.* [https://www.who.int/publications/i/item/who-](https://www.who.int/publications/i/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines)
22 578 [sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines](https://www.who.int/publications/i/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines) (Date last cessed)
- 23
24 579 26. Kerneis S, Launay O, Turbelin C, *et al.*; Long-term Immune Responses to Vaccination in HIV-Infected Patients: A Systematic
25 580 Review and Meta-Analysis. *Clinical Infectious Diseases* 2014;**58**(8):1130-1139
- 26
27 581 27. Association BH. *BHIVA Statement on JCVI recommendations for COVID vaccine Spring 2022 booster dose.*
28 582 <https://www.bhiva.org/BHIVA-community-statement-on-JCVI-recommendations-for-COVID-vaccine-spring-2022-booster-dose> (Date last
29 583 cessed)
- 30
31 584 28. Yang Y, Du L; SARS-CoV-2 spike protein: a key target for eliciting persistent neutralizing antibodies. *Signal Transduction and*
32 585 *Targeted Therapy* 2021;**6**(1)
- 33 586 29. Chen Y, Zuiani A, Fischinger S, *et al.*; Quick COVID-19 Healers Sustain Anti-SARS-CoV-2 Antibody Production. *Cell*
34 587 2020;**183**(6):1496-1507.e16
- 36 588 30. McMahan K, Yu J, Mercado NB, *et al.*; Correlates of protection against SARS-CoV-2 in rhesus macaques. *Nature*
37 589 2021;**590**(7847):630-634
- 38
39 590 31. Yu J, Tostanoski LH, Peter L, *et al.*; DNA vaccine protection against SARS-CoV-2 in rhesus macaques. *Science*
40 591 2020;**369**(6505):806-811
- 41
42
43
44
45
46
47

- 1
2
3 592 32. Deng W, Bao L, Liu J, *et al.*; Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques. *Science*
4 593 2020;**369**(6505):818-823
- 5 594 33. Hall VJ, Foulkes S, Charlett A, *et al.*; SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care
6 595 workers in England: a large, multicentre, prospective cohort study (SIREN). *The Lancet* 2021;**397**(10283):1459-1469
- 8 596 34. Feng S, Phillips DJ, White T, *et al.*; Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nature*
9 597 *Medicine* 2021;**27**(11):2032-2040
- 11 598 35. Castillo-Olivares J, Wells DA, Ferrari M, *et al.*; Analysis of Serological Biomarkers of SARS-CoV-2 Infection in Convalescent
12 599 Samples From Severe, Moderate and Mild COVID-19 Cases. *Frontiers in Immunology* 2021;**12**
- 14 600 36. Lucas C, Klein J, Sundaram M, *et al.*; Kinetics of antibody responses dictate COVID-19 outcome. *medRxiv : the preprint server for*
15 601 *health sciences* 2020:2020.12.18.20248331
- 17 602 37. Zheng J, Deng Y, Zhao Z, *et al.*; Characterization of SARS-CoV-2-specific humoral immunity and its potential applications and
18 603 therapeutic prospects. *Cellular & Molecular Immunology* 2022;**19**(2):150-157
- 19 604 38. Wang Y, Zhang L, Sang L, *et al.*; Kinetics of viral load and antibody response in relation to COVID-19 severity. *Journal of Clinical*
20 605 *Investigation* 2020;**130**(10):5235-5244
- 22 606 39. Siracusano G, Brombin C, Pastori C, *et al.*; Profiling Antibody Response Patterns in COVID-19: Spike S1-Reactive IgA Signature in
23 607 the Evolution of SARS-CoV-2 Infection. *Frontiers in Immunology* 2021;**12**
- 25 608 40. Zhao J, Yuan Q, Wang H, *et al.*; Antibody Responses to SARS-CoV-2 in Patients With Novel Coronavirus Disease 2019. *Clinical*
26 609 *Infectious Diseases* 2020;**71**(16):2027-2034
- 28 610 41. Lou B, Li T-D, Zheng S-F, *et al.*; Serology characteristics of SARS-CoV-2 infection after exposure and post-symptom onset.
29 611 *European Respiratory Journal* 2020;**56**(2):2000763
- 31 612 42. Lynch KL, Whitman JD, Lacanienta NP, *et al.*; Magnitude and Kinetics of Anti-Severe Acute Respiratory Syndrome Coronavirus 2
32 613 Antibody Responses and Their Relationship to Disease Severity. *Clinical Infectious Diseases* 2021;**72**(2):301-308
- 33 614 43. Seow J, Graham C, Merrick B, *et al.*; Longitudinal observation and decline of neutralizing antibody responses in the three months
34 615 following SARS-CoV-2 infection in humans. *Nature Microbiology* 2020;**5**(12):1598-1607
- 36 616 44. Wang Y, Li J, Li H, *et al.*; Persistence of SARS-CoV-2-specific antibodies in COVID-19 patients. *International*
37 617 *immunopharmacology* 2021;**90**:107271-107271
- 39 618 45. Harvey WT, Carabelli AM, Jackson B, *et al.*; SARS-CoV-2 variants, spike mutations and immune escape. *Nature Reviews*
40 619 *Microbiology* 2021;**19**(7):409-424

- 1
2
3 620 46. Baden LR, El Sahly HM, Essink B, *et al.*; Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of*
4 621 *Medicine* 2021;**384**(5):403-416
- 5 622 47. Voysey M, Clemens SAC, Madhi SA, *et al.*; Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-
6 623 2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet* 2021;**397**(10269):99-111
- 8 624 48. Polack FP, Thomas SJ, Kitchin N, *et al.*; Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of*
9 625 *Medicine* 2020;**383**(27):2603-2615
- 10
11 626 49. Khoury DS, Cromer D, Reynaldi A, *et al.*; Neutralizing antibody levels are highly predictive of immune protection from
12 627 symptomatic SARS-CoV-2 infection. *Nature Medicine* 2021;**27**(7):1205-1211
- 13
14 628 50. Feikin Daniel R* HMM, Abu-Raddad Laith J, Andrews Nick, Araos Rafael , Goldberg Yair, Groome Michelle J , Huppert Amit,,
15 629 O'Brien Katherine L SPG, Wilder-Smith Annelies, Zeger Scott, Knoll Maria Deloria*, Patel Minal K*; Duration of effectiveness of
16 630 vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *The Lancet* 2022
17
- 18 631 51. Munro APS, Janani L, Cornelius V, *et al.*; Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster)
19 632 following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2
20 633 trial. *The Lancet* 2021;**398**(10318):2258-2276
- 21
22 634 52. Cromer D, Steain M, Reynaldi A, *et al.*; Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the
23 635 impact of boosting: a meta-analysis. *The Lancet Microbe* 2022;**3**(1):e52-e61
- 24
25 636 53. Jeffery-Smith A, Burton AR, Lens S, *et al.*; SARS-CoV-2-specific memory B cells can persist in the elderly who have lost
26 637 detectable neutralizing antibodies. *Journal of Clinical Investigation* 2022;**132**(2)
- 27 638 54. Wang Z, Muecksch F, Schaefer-Babajew D, *et al.*; Naturally enhanced neutralizing breadth against SARS-CoV-2 one year after
28 639 infection. *Nature* 2021;**595**(7867):426-431
- 30 640 55. Sokal A, Chappert P, Barba-Spaeth G, *et al.*; Maturation and persistence of the anti-SARS-CoV-2 memory B cell response. *Cell*
31 641 2021;**184**(5):1201-1213.e14
- 32
33 642 56. Sakharkar M, Rappazzo CG, Wieland-Alter WF, *et al.*; Prolonged evolution of the human B cell response to SARS-CoV-2 infection.
34 643 *Science Immunology* 2021;**6**(56):eabg6916
- 35
36 644 57. Muecksch F, Weisblum Y, Barnes CO, *et al.*; Affinity maturation of SARS-CoV-2 neutralizing antibodies confers potency, breadth,
37 645 and resilience to viral escape mutations. *Immunity* 2021;**54**(8):1853-1868.e7
- 38
39 646 58. Reyes RA, Clarke K, Gonzales SJ, *et al.*; SARS-CoV-2 spike-specific memory B cells express higher levels of T-bet and FcRL5
40 647 after non-severe COVID-19 as compared to severe disease. *PLOS ONE* 2021;**16**(12):e0261656

- 1
2
3 648 59. Bergamaschi L, Mescia F, Turner L, *et al.*; Longitudinal analysis reveals that delayed bystander CD8+ T cell activation and early
4 649 immune pathology distinguish severe COVID-19 from mild disease. *Immunity* 2021;**54**(6):1257-1275.e8
- 5 650 60. Moss P; The T cell immune response against SARS-CoV-2. *Nature Immunology* 2022;**23**(2):186-193
- 6
7 651 61. Rydzynski Moderbacher C, Ramirez SI, Dan JM, *et al.*; Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19
8 652 and Associations with Age and Disease Severity. *Cell* 2020;**183**(4):996-1012.e19
- 9
10 653 62. Sekine T, Perez-Potti A, Rivera-Ballesteros O, *et al.*; Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or
11 654 Mild COVID-19. *Cell* 2020;**183**(1):158-168.e14
- 12
13 655 63. Zhou R, To KK-W, Wong Y-C, *et al.*; Acute SARS-CoV-2 Infection Impairs Dendritic Cell and T Cell Responses. *Immunity*
14 656 2020;**53**(4):864-877.e5
- 15 657 64. Liao M, Liu Y, Yuan J, *et al.*; Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nature Medicine*
16 658 2020;**26**(6):842-844
- 17
18 659 65. Tan AT, Linster M, Tan CW, *et al.*; Early induction of functional SARS-CoV-2-specific T cells associates with rapid viral clearance
19 660 and mild disease in COVID-19 patients. *Cell Reports* 2021;**34**(6):108728
- 20
21 661 66. Notarbartolo S, Ranzani V, Bandera A, *et al.*; Integrated longitudinal immunophenotypic, transcriptional, and repertoire analyses
22 662 delineate immune responses in patients with COVID-19. *Science Immunology* 2021;**6**(62):eabg5021
- 23
24 663 67. Le Bert N, Tan AT, Kunasegaran K, *et al.*; SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected
25 664 controls. *Nature* 2020;**584**(7821):457-462
- 26
27 665 68. Oberhardt V, Luxenburger H, Kemming J, *et al.*; Rapid and stable mobilization of CD8+ T cells by SARS-CoV-2 mRNA vaccine.
28 666 *Nature* 2021;**597**(7875):268-273
- 29
30 667 69. Soresina A, Moratto D, Chiarini M, *et al.*; Two X-linked agammaglobulinemia patients develop pneumonia as COVID-19
31 668 manifestation but recover. *Pediatric Allergy and Immunology* 2020;**31**(5):565-569
- 32 669 70. Safavi F, Nourbakhsh B, Azimi AR; B-cell depleting therapies may affect susceptibility to acute respiratory illness among patients
33 670 with multiple sclerosis during the early COVID-19 epidemic in Iran. *Multiple Sclerosis and Related Disorders* 2020;**43**:102195
- 34
35 671 71. Montero-Escribano P, Matías-Guiu J, Gómez-Iglesias P, *et al.*; Anti-CD20 and COVID-19 in multiple sclerosis and related disorders:
36 672 A case series of 60 patients from Madrid, Spain. *Multiple Sclerosis and Related Disorders* 2020;**42**:102185
- 37
38 673 72. Bange EM, Han NA, Wileyto P, *et al.*; CD8+ T cells contribute to survival in patients with COVID-19 and hematologic cancer.
39 674 *Nature Medicine* 2021;**27**(7):1280-1289
- 40
41 675 73. Grifoni A, Weiskopf D, Ramirez SI, *et al.*; Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19
42 676 Disease and Unexposed Individuals. *Cell* 2020;**181**(7):1489-1501.e15
- 43
44
45
46
47

- 1
2
3 677 74. Grifoni A, Sidney J, Vita R, *et al.*; SARS-CoV-2 human T cell epitopes: Adaptive immune response against COVID-19. *Cell Host &*
4 678 *Microbe* 2021;**29**(7):1076-1092
- 5 679 75. Peng Y, Felce SL, Dong D, *et al.*; An immunodominant NP105–113-B*07:02 cytotoxic T cell response controls viral replication and
6 680 is associated with less severe COVID-19 disease. *Nature Immunology* 2022;**23**(1):50-61
- 8 681 76. Peng Y, Mentzer AJ, Liu G, *et al.*; Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent
9 682 individuals following COVID-19. *Nature Immunology* 2020;**21**(11):1336-1345
- 11 683 77. Juno JA, Tan H-X, Lee WS, *et al.*; Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19.
12 684 *Nature Medicine* 2020;**26**(9):1428-1434
- 13
14 685 78. Stephenson E, Reynolds G, Botting RA, *et al.*; Single-cell multi-omics analysis of the immune response in COVID-19. *Nature*
15 686 *medicine* 2021;**27**(5):904-916
- 16
17 687 79. Tarke A, Coelho CH, Zhang Z, *et al.*; SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize
18 688 variants from Alpha to Omicron. *Cell* 2022;**185**(5):847-859.e11
- 19 689 80. Liu J, Chandrashekar A, Sellers D, *et al.*; Vaccines Elicit Highly Conserved Cellular Immunity to SARS-CoV-2 Omicron. *Nature*
20 690 2022
- 22 691 81. Swadling L, Diniz MO, Schmidt NM, *et al.*; Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2.
23 692 *Nature* 2022;**601**(7891):110-117
- 24
25 693 82. Schulien I, Kemming J, Oberhardt V, *et al.*; Characterization of pre-existing and induced SARS-CoV-2-specific CD8+ T cells.
26 694 *Nature Medicine* 2021;**27**(1):78-85
- 27
28 695 83. Mateus J, Grifoni A, Tarke A, *et al.*; Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. *Science*
29 696 2020;**370**(6512):89-94
- 30
31 697 84. D W, MP SKR, A G, *et al.*; Phenotype and kinetics of SARS-CoV-specific T cells in COVID-19 patients with acute respiratory
32 698 distress syndrome. *Science Immunology* 2020;**5**(48):2071
- 33 699 85. Braun J, Loyal L, Frensch M, *et al.*; SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. *Nature*
34 700 2020;**587**(7833):270-274
- 36 701 86. Cassaniti I, Percivalle E, Bergami F, *et al.*; SARS-CoV-2 specific T-cell immunity in COVID-19 convalescent patients and
37 702 unexposed controls measured by ex vivo ELISpot assay. *Clinical Microbiology and Infection* 2021;**27**(7):1029-1034
- 38
39 703 87. Killerby ME BH, Haynes A, Dahl RM, Mustaquim D, Gerber SI, Watson JT.; Human coronavirus circulation in the United States
40 704 2014-2017. *J Clin Virol* 2018;**101**:52-56
- 41
42
43
44
45
46
47

- 1
2
3 705 88. Gorse GJ, Patel GB, Vitale JN, *et al.*; Prevalence of Antibodies to Four Human Coronaviruses Is Lower in Nasal Secretions than in
4 706 Serum. *Clinical and Vaccine Immunology* 2010;**17**(12):1875-1880
- 5 707 89. Walsh EE, Shin JH, Falsey AR; Clinical Impact of Human Coronaviruses 229E and OC43 Infection in Diverse Adult Populations.
6 708 *Journal of Infectious Diseases* 2013;**208**(10):1634-1642
- 8 709 90. Guo L, Wang Y, Kang L, *et al.*; Cross-reactive antibody against human coronavirus OC43 spike protein correlates with disease
9 710 severity in COVID-19 patients: a retrospective study. *Emerging Microbes & Infections* 2021;**10**(1):664-676
- 11 711 91. Kundu R, Narean JS, Wang L, *et al.*; Cross-reactive memory T cells associate with protection against SARS-CoV-2 infection in
12 712 COVID-19 contacts. *Nature Communications* 2022;**13**(1)
- 13
14 713 92. Oja AE, Saris A, Ghandour CA, *et al.*; Divergent SARS-CoV-2-specific T- and B-cell responses in severe but not mild COVID-19
15 714 patients. *European Journal of Immunology* 2020;**50**(12):1998-2012
- 16
17 715 93. Gelarden I, Nguyen J, Gao J, *et al.*; Comprehensive evaluation of bronchoalveolar lavage from patients with severe COVID-19 and
18 716 correlation with clinical outcomes. *Human pathology* 2021;**113**:92-103
- 19 717 94. Smith N, Goncalves P, Charbit B, *et al.*; Distinct systemic and mucosal immune responses during acute SARS-CoV-2 infection.
20 718 *Nature Immunology* 2021;**22**(11):1428-1439
- 22 719 95. Wright PF, Prevost-Reilly, A.C., Natarajan, H., Brickley, E.B., Connor, R.I., Wieland-Alter, W.F., Miele, A.S., Weiner, J.A.,
23 720 Nerenz, R.D., Ackerman, M.E. ...; Longitudinal Systemic and Mucosal Immune Responses to SARS-CoV-2 Infection. *The Journal of*
24 721 *Infectious Diseases* 2022
- 26 722 96. Chan RWY, Liu S, Cheung JY, *et al.*; The Mucosal and Serological Immune Responses to the Novel Coronavirus (SARS-CoV-2)
27 723 Vaccines. *Frontiers in Immunology* 2021;**12**
- 28
29 724 97. Azzi L, Dalla Gasperina D, Veronesi G, *et al.*; Mucosal immune response in BNT162b2 COVID-19 vaccine recipients.
30 725 *eBioMedicine* 2022;**75**:103788
- 31
32 726 98. Sano K, Bhavsar D, Singh G, *et al.*; Efficient mucosal antibody response to SARS-CoV-2 vaccination is induced in previously
33 727 infected individuals. Cold Spring Harbor Laboratory, 2021.
- 34
35 728 99. Asowata OE, Singh A, Ngoepe A, *et al.*; Irreversible depletion of intestinal CD4+ T cells is associated with T cell activation during
36 729 chronic HIV infection. *JCI Insight* 2021;**6**(22)
- 37 730 100. Guadalupe M, Reay E, Sankaran S, *et al.*; Severe CD4 + T-Cell Depletion in Gut Lymphoid Tissue during Primary Human
38 731 Immunodeficiency Virus Type 1 Infection and Substantial Delay in Restoration following Highly Active Antiretroviral Therapy. *Journal of*
39 732 *Virology* 2003;**77**(21):11708-11717
- 41
42
43
44
45
46
47

- 1
2
3 733 101. Hunt PW, Lee SA, Siedner MJ; Immunologic Biomarkers, Morbidity, and Mortality in Treated HIV Infection. *Journal of Infectious*
4 734 *Diseases* 2016;**214**(suppl 2):S44-S50
- 5 735 102. Smith R, de Boer R, Brul S, *et al.*; Premature and accelerated aging: HIV or HAART? *Frontiers in Genetics* 2013;**3**
6
- 7 736 103. Deeks SG, Phillips AN; HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ* 2009;**338**:a3172
8
- 9 737 104. Erlandson KM KM; HIV and Aging: Reconsidering the Approach to Management of Comorbidities. *Infect Dis Clin North Am*
10 738 2019;**33**(3)
- 11 739 105. Fenwick C, Joo V, Jacquier P, *et al.*; T-cell exhaustion in HIV infection. *Immunological Reviews* 2019;**292**(1):149-163
12
- 13 740 106. Sabado RL, O'Brien M, Subedi A, *et al.*; Evidence of dysregulation of dendritic cells in primary HIV infection. *Blood*
14 741 2010;**116**(19):3839-3852
15
- 16 742 107. Bussmann BM RS, Bieniek B, Krznaric I, Ackermann F, Jassoy C. ; Loss of HIV-specific memory B-cells as a potential mechanism
17 743 for the dysfunction of the humoral immune response against HIV. *Virology* 2010;**397**(1):7-13
18
- 19 744 108. Kardava L, Moir S, Wang W, *et al.*; Attenuation of HIV-associated human B cell exhaustion by siRNA downregulation of inhibitory
20 745 receptors. *Journal of Clinical Investigation* 2011;**121**(7):2614-2624
- 21 746 109. Moir S, Fauci AS; B-cell responses to HIV infection. *Immunological reviews* 2017;**275**(1):33-48
22
- 23 747 110. Bart P-A, Rizzardi GP, Tambussi G, *et al.*; Immunological and virological responses in HIV-1-infected adults at early stage of
24 748 established infection treated with highly active antiretroviral therapy. *AIDS* 2000;**14**(13)
- 26 749 111. Group TISS; Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *New England Journal of Medicine*
27 750 2015;**373**(9):795-807
28
- 29 751 112. Pallikkuth S, de Armas L, Rinaldi S, *et al.*; T Follicular Helper Cells and B Cell Dysfunction in Aging and HIV-1 Infection.
30 752 *Frontiers in immunology* 2017;**8**:1380-1380
- 31 753 113. Deeks SG, Tracy R, Douek DC; Systemic Effects of Inflammation on Health during Chronic HIV Infection. *Immunity*
32 754 2013;**39**(4):633-645
- 34 755 114. Margolick JB, Bream JH, Martínez-Maza O, *et al.*; Frailty and Circulating Markers of Inflammation in HIV+ and HIV- Men in the
35 756 Multicenter AIDS Cohort Study. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 2017;**74**(4):407-417
- 37 757 115. Triplette M, Justice A, Attia EF, *et al.*; Markers of chronic obstructive pulmonary disease are associated with mortality in people
38 758 living with HIV. *AIDS* 2018;**32**(4):487-493
39
- 40 759 116. Costiniuk CT, Jenabian M-A; The lungs as anatomical reservoirs of HIV infection. *Reviews in Medical Virology* 2014;**24**(1):35-54
41
42
43
44
45
46
47

- 1
2
3 760 117. Shiels MS, Cole SR, Kirk GD, *et al.*; A Meta-Analysis of the Incidence of Non-AIDS Cancers in HIV-Infected Individuals. *JAIDS*
4 761 *Journal of Acquired Immune Deficiency Syndromes* 2009;**52**(5):611-622
- 5 762 118. Kirk GD, Merlo C, O'Driscoll P, *et al.*; HIV Infection Is Associated with an Increased Risk for Lung Cancer, Independent of
6 763 Smoking. *Clinical Infectious Diseases* 2007;**45**(1):103-110
- 8 764 119. Alexandrova Y, Costiniuk CT, Jenabian M-A; Pulmonary Immune Dysregulation and Viral Persistence During HIV Infection.
9 765 *Frontiers in Immunology* 2022;**12**
- 10
11 766 120. Brown J, Pickett E, Smith C, *et al.*; The effect of HIV status on the frequency and severity of acute respiratory illness. *PLOS ONE*
12 767 2020;**15**(5):e0232977
- 13
14 768 121. Pallikkuth S, De Armas LR, Pahwa R, *et al.*; Impact of aging and HIV infection on serologic response to seasonal influenza
15 769 vaccination. *AIDS* 2018;**32**(9):1085-1094
- 16
17 770 122. George VK, Pallikkuth S, Parmigiani A, *et al.*; HIV infection Worsens Age-Associated Defects in Antibody Responses to Influenza
18 771 Vaccine. *Journal of Infectious Diseases* 2015;**211**(12):1959-1968
- 19 772 123. Bonetti TC SR, Weckx LY, Tavares-Lopes L, de Moraes-Pinto MI; Tetanus and diphtheria antibodies and response to a booster dose
20 773 in Brazilian HIV-1-infected women. *Vaccine* 2004;**22** (27-28):3707-12
- 22 774 124. Avelino-Silva VI, Miyaji KT, Hunt PW, *et al.*; CD4/CD8 Ratio and KT Ratio Predict Yellow Fever Vaccine Immunogenicity in
23 775 HIV-Infected Patients. *PLOS Neglected Tropical Diseases* 2016;**10**(12):e0005219
- 24
25 776 125. Kroon FP, Van Dissel JT, Labadie J, *et al.*; Antibody Response to Diphtheria, Tetanus, and Poliomyelitis Vaccines in Relation to the
26 777 Number of CD4+ T Lymphocytes in Adults Infected with Human Immunodeficiency Virus. *Clinical Infectious Diseases* 1995;**21**(5):1197-
27 778 1203
- 28
29 779 126. Rees-Spear C, McCoy LE; Vaccine responses in ageing and chronic viral infection. *Oxford Open Immunology* 2021;**2**(1)
- 30
31 780 127. Goronzy JJ, Weyand CM; Understanding immunosenescence to improve responses to vaccines. *Nature Immunology* 2013;**14**(5):428-
32 781 436
- 33 782 128. Rinaldi S, Pallikkuth S, George VK, *et al.*; Paradoxical aging in HIV: immune senescence of B Cells is most prominent in young
34 783 age. *Aging* 2017;**9**(4):1307-1325
- 36 784 129. Chauvin M, Sauce D; Mechanisms of immune aging in HIV. *Clinical Science* 2022;**136**(1):61-80
- 37
38 785 130. Walsh EE, Frenck RW, Falsey AR, *et al.*; Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *New*
39 786 *England Journal of Medicine* 2020;**383**(25):2439-2450
- 40
41 787 131. Torres I, Albert E, Giménez E, *et al.*; B- and T-cell immune responses elicited by the Comirnaty® COVID-19 vaccine in nursing-
42 788 home residents. *Clinical Microbiology and Infection* 2021;**27**(11):1672-1677
- 43
44
45
46
47

- 1
2
3 789 132. Zhu F-C, Guan X-H, Li Y-H, *et al.*; Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in
4 790 healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet* 2020;**396**(10249):479-488
- 5 791 133. Li J, Hui A, Zhang X, *et al.*; Safety and immunogenicity of the SARS-CoV-2 BNT162b1 mRNA vaccine in younger and older
6 792 Chinese adults: a randomized, placebo-controlled, double-blind phase 1 study. *Nature Medicine* 2021;**27**(6):1062-1070
- 8 793 134. Anderson EJ, Roupheal NG, Widge AT, *et al.*; Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults.
9 794 *New England Journal of Medicine* 2020;**383**(25):2427-2438
- 10
11 795 135. Collier DA, Ferreira IATM, Kotagiri P, *et al.*; Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2.
12 796 *Nature* 2021;**596**(7872):417-422
- 13
14 797 136. De Francesco D, Wit FW, Bürkle A, *et al.*; Do people living with HIV experience greater age advancement than their HIV-negative
15 798 counterparts? *AIDS* 2019;**33**(2):259-268
- 16
17 799 137. Royston L, Isnard S, Lin J, *et al.*; Cytomegalovirus as an Uninvited Guest in the Response to Vaccines in People Living with HIV.
18 800 *Viruses* 2021;**13**(7):1266
- 19 801 138. Perello R, Vergara A, Monclus E, *et al.*; Cytomegalovirus infection in HIV-infected patients in the era of combination antiretroviral
20 802 therapy. *BMC Infectious Diseases* 2019;**19**(1)
- 22 803 139. Fuster F, Vargas JI, Jensen D, *et al.*; CD4/CD8 ratio as a predictor of the response to HBV vaccination in HIV-positive patients: A
23 804 prospective cohort study. *Vaccine* 2016;**34**(16):1889-1895
- 24
25 805 140. Hadrup SR, Strindhall J, Køllgaard T, *et al.*; Longitudinal Studies of Clonally Expanded CD8 T Cells Reveal a Repertoire Shrinkage
26 806 Predicting Mortality and an Increased Number of Dysfunctional Cytomegalovirus-Specific T Cells in the Very Elderly. *The Journal of*
27 807 *Immunology* 2006;**176**(4):2645-2653
- 28
29 808 141. Spinelli MA, Lynch KL, Yun C, *et al.*; SARS-CoV-2 seroprevalence, and IgG concentration and pseudovirus neutralising antibody
30 809 titres after infection, compared by HIV status: a matched case-control observational study. *The Lancet HIV* 2021;**8**(6):e334-e341
- 31
32 810 142. Alrubayyi A, Gea-Mallorquí E, Touizer E, *et al.*; Characterization of humoral and SARS-CoV-2 specific T cell responses in people
33 811 living with HIV. *Nature Communications* 2021;**12**(1)
- 34
35 812 143. Snyman J, Sanders EJ, Ndung'u T; COVID-19 in Africa: preexisting immunity and HIV. *AIDS (London, England)*
36 813 2021;**35**(14):2391-2393
- 37 814 144. Pallikkuth S SM, Beauchamps L, Raccamarich P, Uribe C, Salazar A, Pallin M, Varghese E, Roach M, Mantero A, Pahwa S, Jones
38 815 Weiss D, Alcaide ML.; Persistence of SARS-CoV-2 –specific AB response in HIV+ individuals on ART. *Conference on Retroviruses and*
39 816 *Opportunistic Infections: Topics in Antiviral Medicine*, 2021, 88.

- 1
2
3 817 145. Riddell AC, Kele B, Harris K, *et al.*; Generation of novel SARS-CoV-2 variants on B.1.1.7 lineage in three patients with advanced
4 818 HIV disease. *Clinical Infectious Diseases* 2022
- 5 819 146. Sharov KS; HIV/SARS-CoV-2 co-infection: T cell profile, cytokine dynamics and role of exhausted lymphocytes. *International*
6 820 *journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2021;**102**:163-169
- 8 821 147. Khan K, Lustig G, Bernstein M, *et al.*; Immunogenicity of SARS-CoV-2 infection and Ad26.CoV2.S vaccination in people living
9 822 with HIV. *Clinical Infectious Diseases* 2021:ciab1008
- 11 823 148. Riou C, Du Bruyn E, Stek C, *et al.*; Relationship of SARS-CoV-2-specific CD4 response to COVID-19 severity and impact of HIV-
12 824 1 and tuberculosis coinfection. *Journal of Clinical Investigation* 2021;**131**(12)
- 14 825 149. Bhaskaran K, Rentsch CT, Mackenna B, *et al.*; HIV infection and COVID-19 death: a population-based cohort analysis of UK
15 826 primary care data and linked national death registrations within the OpenSAFELY platform. *The Lancet HIV* 2021;**8**(1):e24-e32
- 16 827 150. Etienne N, Karmochkine M, Slama L, *et al.*; HIV infection and COVID-19: risk factors for severe disease. *AIDS (London, England)*
18 828 2020;**34**(12):1771-1774
- 19 829 151. Riddell AC, Kele B, Harris K, *et al.*; Generation of novel SARS-CoV-2 variants on B.1.1.7 lineage in three patients with advanced
20 830 HIV disease. Cold Spring Harbor Laboratory, 2022.
- 22 831 152. Maponga T JM, Tegally H *et al.*; Persistent SARS-CoV-2 infection with accumulation of mutations in a patient with poorly
23 832 controlled HIV infection. *MedRxiv* 2021
- 25 833 153. Cele S, Karim F, Lustig G, *et al.*; SARS-CoV-2 prolonged infection during advanced HIV disease evolves extensive immune escape.
26 834 *Cell Host & Microbe* 2022;**30**(2):154-162.e5
- 28 835 154. Robson F, Khan KS, Le TK, *et al.*; Coronavirus RNA Proofreading: Molecular Basis and Therapeutic Targeting. *Molecular Cell*
29 836 2020;**79**(5):710-727
- 31 837 155. Karim F, Moosa MY, Gosnell B, *et al.*; Persistent SARS-CoV-2 infection and intra-host evolution in association with advanced HIV
32 838 infection. Cold Spring Harbor Laboratory, 2021.
- 33 839 156. Peluso MJ, Spinelli MA, Deveau T-M, *et al.*; POST-ACUTE SEQUELAE AND ADAPTIVE IMMUNE RESPONSES IN PEOPLE
34 840 LIVING WITH HIV RECOVERING FROM SARS-COV-2 INFECTION. Cold Spring Harbor Laboratory, 2022.
- 36 841 157. Pujari S, Gaikwad S, Chitalikar A, *et al.*; Long-coronavirus disease among people living with HIV in western India: An
37 842 observational study. *Immunity, Inflammation and Disease* 2021;**9**(3):1037-1043
- 39 843 158. Luxi N, Giovanazzi A, Capuano A, *et al.*; COVID-19 Vaccination in Pregnancy, Paediatrics, Immunocompromised Patients, and
40 844 Persons with History of Allergy or Prior SARS-CoV-2 Infection: Overview of Current Recommendations and Pre- and Post-Marketing
41 845 Evidence for Vaccine Efficacy and Safety. *Drug Safety* 2021;**44**(12):1247-1269
- 42
43
44
45
46
47

- 1
2
3 846 159. Shinde V, Bhikha S, Hoosain Z, *et al.*; Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant. *New England*
4 847 *Journal of Medicine* 2021;**384**(20):1899-1909
- 5 848 160. Feng Y, Zhang Y, He Z, *et al.*; Immunogenicity of an inactivated SARS-CoV-2 vaccine in people living with HIV-1: a non-
6 849 randomized cohort study. *eClinicalMedicine* 2022;**43**:101226
- 8 850 161. Sadoff J, Gray G, Vandebosch A, *et al.*; Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *New England*
9 851 *Journal of Medicine* 2021;**384**(23):2187-2201
- 11 852 162. WHO. *Background document on the Janssen Ad26.COV2.S (COVID-19) vaccine: background document to the WHO Interim*
12 853 *recommendations for use of Ad26.COV2.S (COVID-19) vaccine.* <https://apps.who.int/iris/handle/10665/340180> (Date last cessed)
- 13
14 854 163. Tamuzi JL, Muyaya LM, Mitra A, *et al.*; Systematic review and meta-analysis of COVID-19 vaccines safety, tolerability, and
15 855 efficacy among HIV-infected patients. Cold Spring Harbor Laboratory, 2022.
- 16
17 856 164. Levy I, Wieder-Finesod A, Litchevsky V, *et al.*; Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in people
18 857 living with HIV-1. *Clinical Microbiology and Infection* 2021;**27**(12):1851-1855
- 19 858 165. Bozzi G, Lombardi A, Ludovisi S, *et al.*; Transient increase in plasma HIV RNA after COVID-19 vaccination with mRNA-1272.
20 859 *International Journal of Infectious Diseases* 2021;**113**:125-126
- 22 860 166. Yek C, Gianella S, Plana M, *et al.*; Standard vaccines increase HIV-1 transcription during antiretroviral therapy. *AIDS (London,*
23 861 *England)* 2016;**30**(15):2289-2298
- 24
25 862 167. Nault L, Marchitto L, Goyette G, *et al.*; Covid-19 vaccine immunogenicity in people living with HIV-1. Cold Spring Harbor
26 863 Laboratory, 2021.
- 27
28 864 168. Jedicke N, Stankov MV, Cossmann A, *et al.*; Humoral immune response following prime and boost BNT162b2 vaccination in people
29 865 living with HIV on antiretroviral therapy. *HIV Medicine* 2021
- 30
31 866 169. Brumme ZL, Mwimanzi F, Lapointe HR, *et al.*; Humoral immune responses to COVID-19 vaccination in people living with HIV
32 867 receiving suppressive antiretroviral therapy. *medRxiv : the preprint server for health sciences*: Cold Spring Harbor Laboratory, 2021,
33 868 2021.10.03.21264320.
- 34
35 869 170. Bergman P, Blennow O, Hansson L, *et al.*; Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five
36 870 groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial. *eBioMedicine* 2021;**74**:103705
- 37 871 171. Ruddy JA, Boyarsky BJ, Bailey JR, *et al.*; Safety and antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in
38 872 persons with HIV. *AIDS* 2021;**35**(14)
- 40
41
42
43
44
45
46
47

- 1
2
3 873 172. Lombardi A, Butta GM, Donnici L, *et al.*; Anti-spike antibodies and neutralising antibody activity in people living with HIV
4 874 vaccinated with COVID-19 mRNA-1273 vaccine: a prospective single-centre cohort study. *The Lancet regional health. Europe*
5 875 2022;**13**:100287-100287
- 6
7 876 173. Woldemeskel BA, Karaba AH, Garliss CC, *et al.*; The BNT162b2 mRNA Vaccine Elicits Robust Humoral and Cellular Immune
8 877 Responses in People Living With Human Immunodeficiency Virus (HIV). *Clinical Infectious Diseases* 2022;**74**(7):1268-1270
- 9
10 878 174. Woldemeskel BA, Garliss CC, Blankson JN; SARS-CoV-2 mRNA vaccines induce broad CD4+ T cell responses that recognize
11 879 SARS-CoV-2 variants and HCoV-NL63. *Journal of Clinical Investigation* 2021;**131**(10)
- 12 880 175. A. Antinori SC, S. Meschi, V. Bordoni, P. Lorenzini, A. Vergori, S. Lanini, L. De Pascale, G. Matusali, D. Mariotti, C. Cerini, C.
13 881 Candela, P. Galli, V. Puro, C. Castilletti, C. Agrati, E. Girardi, F. Vaia; Immunogenicity of mRNA vaccination against SARS-CoV-2 in
14 882 persons living with HIV (PLWHs) with low CD4 count or previous AIDS. *18th European AIDS Conference* London, 2021.
- 15
16 883 176. Whitaker HJ, Tsang RSM, Byford R, *et al.*; Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune
17 884 response among individuals in clinical risk groups. *Journal of Infection* 2022
- 18
19 885 177. Hensley K S JM, Geurts van Kessel CH, Dalm VA, den Hollander JG, 2 ,Bierman WFW, Leyten EM, Schippers EF, Ammerlaan HS,
20 886 Van der Valk M, Rijnders BJ, Brinkman K , Anna Roukens A, Rokx C; SARS-CoV-2 VACCINE IMMUNOGENICITY IN PLWH IN THE
21 887 NETHERLANDS. *CROI*, 2022.
- 22
23 888 178. Cicalini S VA, Cozzi-Lepri A, Meschi S, Bordoni V, Lanini S, Lapa D, Mariotti D, De Pascal L, LD'aquila V, Castilletti C, Agrati
24 889 CGirardi E, Vaia F, Antinori A; DURABILITY OF SARS-CoV-2 mRNA VACCINE IMMUNE RESPONSE IN PLWH WITH
25 890 ADVANCED DISEASE. *CROI*, 2022.
- 26
27 891 179. Ferrari L PL, Caldara F, Andreassi E, Bertoli A, Austin H, Meloni D, Teti E, Compagno M, Iannetta M, Ceccherini-Silberstein F,
28 892 Sarmati L , Andreoni M, Geretti AM, ; HOW HIV MODULATES THE SAFETY AND IMMUNOGENICITY OF THE BNT162b2
29 893 COVID-19 VACCINE. *CROI*, 2022.
- 30
31 894 180. Pourcher V BL, Soulie C1 , Michelle Rosenzweig M, Marot S, Lacombe K, Valin N, Pialoux G, Calin R, Tubiana R, Valantin MA,
32 895 Klatzmann D, Calvez V, Simon-Tillaux N, Marcelin AG.; HIGH SEROCONVERSION RATE AND DELTA NEUTRALIZATION IN
33 896 PLWHIV VACCINATED WITH BNT162b2 *CROI*, 2022.
- 34
35 897 181. Vergori A CS, Cozzi-Lepri A, Matusali G, Bordoni V, Lanini S, Colavita F, Cimini E, Iannazzo R, De Pascale L, Concetta Castilletti
36 898 C, Chiara A, Girardi E, Vaia F, Antinori A.; IMMUNOGENICITY TO COVID-19 mRNA VACCINE BOOSTER SHOT IN PLWH BY
37 899 CURRENT CD4+ COUNT. 2022.
- 38
39 900 182. Madhi SA, Koen AL, Izu A, *et al.*; Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2
40 901 in people living with and without HIV in South Africa: an interim analysis of a randomised, double-blind, placebo-controlled, phase 1B/2A
41 902 trial. *The Lancet HIV* 2021;**8**(9):e568-e580
- 42
43
44
45
46
47

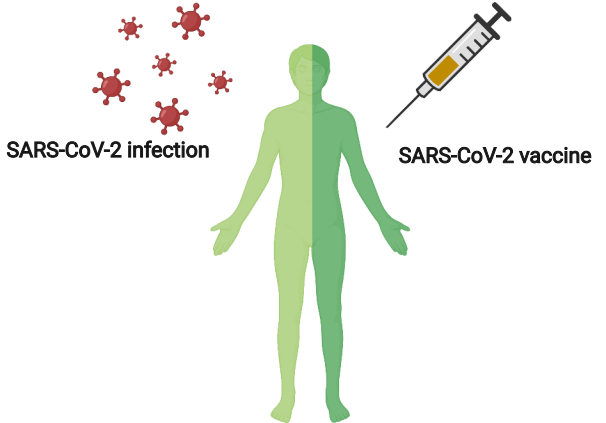
- 1
2
3 903 183. Frater J, Ewer KJ, Ogbe A, *et al.*; Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2
4 904 in HIV infection: a single-arm substudy of a phase 2/3 clinical trial. *The Lancet HIV* 2021;**8**(8):e474-e485
- 5 905 184. Ane T, Ogbe MP, Mustapha Bittaye, Stephanie Longet, Tom Tipton, Wanwisa Dejnirattisai, Katie J. Ewer, Gavin R. Screaton,
6 906 Sarah C. Gilbert, Miles Carroll, Andrew J. Pollard, Sarah Fidler, Julie Fox, Teresa Lambe, John Frater ChAdOx1 nCoV-19
7 907 VACCINATION IN PWH: IMMUNE RESPONSES TO SARS-CoV-2, VOCs, AND HCoVs *CROI*, 2022.
- 9 908 185. Ogbe A, Pace M, Bittaye M, *et al.*; Durability of ChAdOx1 nCov-19 vaccination in people living with HIV. *JCI Insight* 2022
10
11 909 186. Deming ME, Lyke KE; A 'mix and match' approach to SARS-CoV-2 vaccination. *Nature Medicine* 2021;**27**(9):1510-1511
12
13 910 187. Spencer AJ, McKay PF, Belij-Rammerstorfer S, *et al.*; Heterologous vaccination regimens with self-amplifying RNA and adenoviral
14 911 COVID vaccines induce robust immune responses in mice. *Nature Communications* 2021;**12**(1)
- 15 912 188. Barros-Martins J, Hammerschmidt SI, Cossmann A, *et al.*; Immune responses against SARS-CoV-2 variants after heterologous and
16 913 homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. *Nature Medicine* 2021;**27**(9):1525-1529
- 18 914 189. Atmar RL, Lyke KE, Deming ME, *et al.*; Homologous and Heterologous Covid-19 Booster Vaccinations. *New England Journal of*
19 915 *Medicine* 2022
- 21 916 190. Schmidt T, Klemis V, Schub D, *et al.*; Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination.
22 917 *Nature Medicine* 2021;**27**(9):1530-1535
23
- 24 918 191. Borobia AM, Carcas AJ, Pérez-Olmeda M, *et al.*; Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed
25 919 participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. *The Lancet* 2021;**398**(10295):121-130
26
- 27 920 192. Stuart ASV, Shaw RH, Liu X, *et al.*; Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination
28 921 incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-
29 922 inferiority trial. *The Lancet* 2022;**399**(10319):36-49
- 30
31 923 193. Sun J, Zheng Q, Madhira V, *et al.*; Association Between Immune Dysfunction and COVID-19 Breakthrough Infection After SARS-
32 924 CoV-2 Vaccination in the US. *JAMA Internal Medicine* 2022;**182**(2):153
- 33 925 194. Coburn SB, Humes E, Lang R, *et al.*; COVID-19 infections post-vaccination by HIV status in the United States. Cold Spring Harbor
34 926 Laboratory, 2021.
- 36 927 195. Garcia-Beltran WF, St Denis KJ, Hoelzemer A, *et al.*; mRNA-based COVID-19 vaccine boosters induce neutralizing immunity
37 928 against SARS-CoV-2 Omicron variant. *Cell* 2022;**185**(3):457-466.e4
38
- 39 929 196. Hyseni I, Molesti E, Benincasa L, *et al.*; Characterisation of SARS-CoV-2 Lentiviral Pseudotypes and Correlation between
40 930 Pseudotype-Based Neutralisation Assays and Live Virus-Based Micro Neutralisation Assays. *Viruses* 2020;**12**(9):1011
41
42
43
44
45
46
47

- 1
2
3 931 197. Cantoni D, Mayora-Neto M, Temperton N; The role of pseudotype neutralization assays in understanding SARS CoV-2. *Oxford*
4 932 *open immunology* 2021;**2**(1):iqab005-iqab005
- 5 933 198. Valcourt EJ, Manguiat K, Robinson A, *et al.*; Evaluation of a commercially-available surrogate virus neutralization test for severe
6 934 acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *Diagnostic Microbiology and Infectious Disease* 2021;**99**(4):115294
- 8 935 199. Lake DF, Roeder AJ, Kaleta E, *et al.*; Development of a rapid point-of-care test that measures neutralizing antibodies to SARS-CoV-
9 936 2. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology* 2021;**145**:105024-105024
- 11 937 200. Guan L, Yu Y, Wu X, *et al.*; The first Chinese national standards for SARS-CoV-2 neutralizing antibody. *Vaccine*
12 938 2021;**39**(28):3724-3730
- 14 939 201. Huang D, Tran JT, Peng L, *et al.*; A Rapid Assay for SARS-CoV-2 Neutralizing Antibodies That Is Insensitive to Antiretroviral
15 940 Drugs. *The Journal of Immunology* 2021;**207**(1):344-351
- 17 941 202. Angyal A, Longet S, Moore SC, *et al.*; T-cell and antibody responses to first BNT162b2 vaccine dose in previously infected and
18 942 SARS-CoV-2-naive UK health-care workers: a multicentre prospective cohort study. *The Lancet Microbe* 2022;**3**(1):e21-e31
- 19 943 203. Keeton R, Richardson SI, Moyo-Gwete T, *et al.*; Prior infection with SARS-CoV-2 boosts and broadens Ad26.COVS.S
20 944 immunogenicity in a variant-dependent manner. *Cell host & microbe* 2021;**29**(11):1611-1619.e5
- 22 945 204. Velavan TP, Meyer CG, Esen M, *et al.*; COVID-19 and syndemic challenges in ‘Battling the Big Three’: HIV, TB and malaria.
23 946 *International Journal of Infectious Diseases* 2021;**106**:29-32
- 25 947 205. Zumla A, Chan JFW, Azhar EI, *et al.*; Coronaviruses — drug discovery and therapeutic options. *Nature Reviews Drug Discovery*
26 948 2016;**15**(5):327-347
- 28 949 206. Schoergenhofer C, Jilma B, Stimpfl T, *et al.*; Pharmacokinetics of Lopinavir and Ritonavir in Patients Hospitalized With
29 950 Coronavirus Disease 2019 (COVID-19). *Annals of Internal Medicine* 2020;**173**(8):670-672
- 31 951 207. Consortium WST; Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. *New England Journal of*
32 952 *Medicine* 2021;**384**(6):497-511
- 33 953 208. Mohareb AM, Kim AY; Hepatitis B Vaccination in People Living With HIV—If at First You Don’t Succeed, Try Again. *JAMA*
34 954 *Network Open* 2021;**4**(8):e2121281
- 36 955 209. Lacey CJ; HPV vaccination in HIV infection. *Papillomavirus research (Amsterdam, Netherlands)* 2019;**8**:100174-100174
- 38 956 210. Cantoni D, Mayora-Neto M, Nadesalingam A, *et al.*; Neutralisation Hierarchy of SARS-CoV-2 Variants of Concern Using
39 957 Standardised, Quantitative Neutralisation Assays Reveals a Correlation With Disease Severity; Towards Deciphering Protective Antibody
40 958 Thresholds. *Frontiers in Immunology* 2022;**13**
- 41
42
43
44
45
46
47

- 1
2
3 959 211. Cheng SMS, Mok CKP, Leung YWY, *et al.*; Neutralizing antibodies against the SARS-CoV-2 Omicron variant BA.1 following
4 960 homologous and heterologous CoronaVac or BNT162b2 vaccination. *Nature Medicine* 2022;**28**(3):486-489
- 5 961 212. Zou S WM, Ming F, Songjie Wu, Wei Guo, Gifty Marley, Zhongyuan Xing, Zhiyue Zhang, Minxia Zeng, Chao Sun, Jianfeng
6 962 Zhang, Weiming Tang, Ke Liang Immune response and safety to inactivated COVID19 vaccine: A comparison between People Living with
7 963 HIV and HIV-naive individuals. Pre-print paper (2021), available at. *Research Square* 2021
- 9 964 213. Lv Z, Li Q, Feng Z, *et al.*; Inactivated SARS-CoV-2 vaccines elicit immunogenicity and T-cell responses in people living with HIV.
10 965 *International Immunopharmacology* 2022;**102**:108383
- 12
13 966
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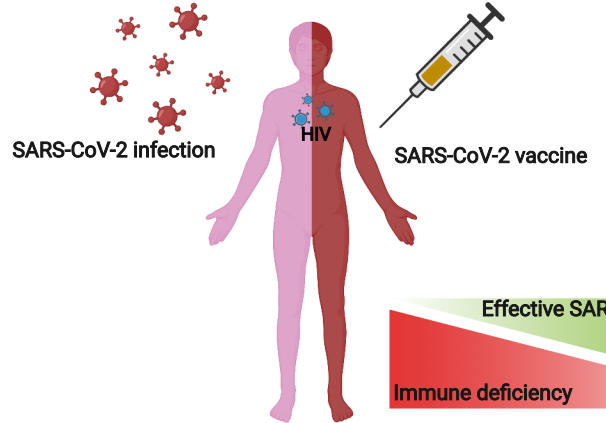


Healthy individuals

Exposure to SARS-CoV-2 antigen through natural infection or vaccination induce immune memory responses against SARS-CoV-2

- ① Innate immune cells are activated after antigen exposure
- ② Antigen presenting cells activate naive T cells in lymphoid organs
- ③ Effective memory T/B cells and antibodies are induced

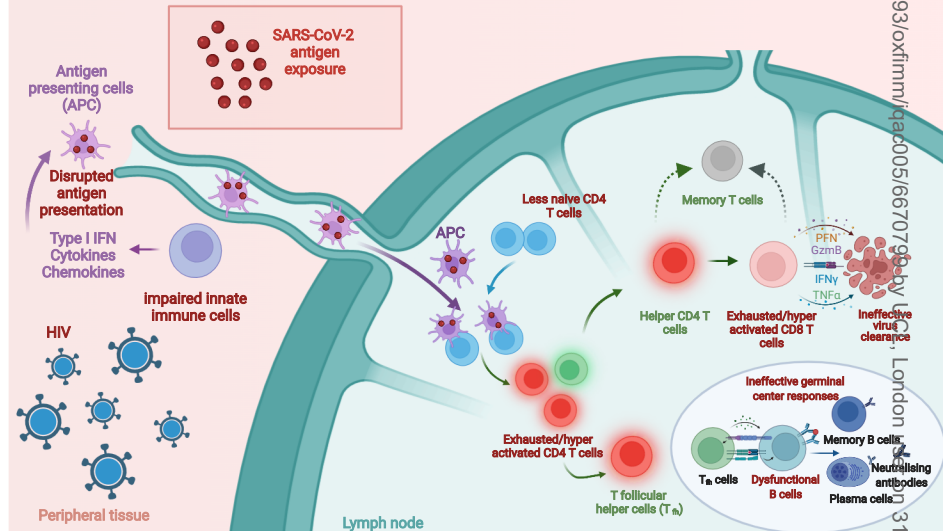
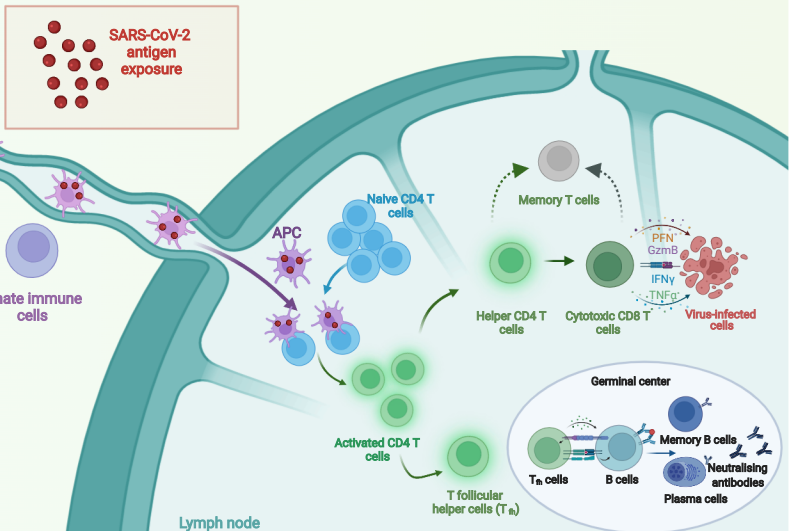
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People living with HIV-1 (PLWH)

Exposure to SARS-CoV-2 antigen through natural infection or vaccination induce suboptimal immune memory responses against SARS-CoV-2

- ① Impaired Innate immune cell triggering
- ② Dysregulated antigen presentation and exhausted adaptive immune responses
- ③ Altered memory T/B cell and antibody responses



Protective SARS-CoV-2 immune responses

Suboptimal SARS-CoV-2 immune responses ?

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