Trends in Immunology

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Feature Review

SARS-CoV-2 humoral immunity in people living with HIV-1

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The effect of COVID-19 on the high number of immunocompromised people living with HIV-1 (PLWH), particularly in Africa, remains a critical concern. Here, we identify key areas that still require further investigation, by examining COVID-19 vaccine effectiveness, and understanding antibody responses in SARS-CoV-2 infection and vaccination in comparison with people without HIV-1 (PWOH). We also assess the potential impact of pre-existing immunity against endemic human coronaviruses on SARS-CoV-2 responses in these individuals. Lastly, we discuss the consequences of persistent infection in PLWH (or other immunocompromised individuals), including prolonged shedding, increased viral diversity within the host, and the implications on SARS-CoV-2 evolution in Africa.

PLWH are a key population vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

Since December 2019, a novel coronavirus pandemic caused by **SARS-CoV-2** (see Glossary) has resulted, to date, in more than 770 million infections and over 7 million deaths worldwide. South Africa accounts for the majority of reported SARS-CoV-2 cases in Africa with over 4 million infections and 100 000 deaths[i]. During the emergence of SARS-CoV-2, a major public health concern was whether the pandemic could disproportionately affect **PLWH**, a key immunocompromised population (Figure 1). There are approximately 40 million PLWH worldwide, with sub-Saharan Africa being the most heavily impacted by HIV-1 infection and accounting for two-thirds of this population[ii]. Of particular concern during the coronavirus disease 2019 (COVID-19) pandemic was the estimated 8.5 million PLWH in South Africa, among which only 75% were accessing **antiretroviral treatment (ART)**[iii]. This means that more than 2 million individuals in South Africa alone are not virally suppressed and are likely to be highly immunocompromised[iii] [1]. Furthermore, this vulnerable population expanded during the COVID-19 pandemic with ART stockouts and the reluctance of patients to seek healthcare [2]. Additionally, PLWH exhibit impaired immune responses to several respiratory infections and respond poorly to vaccination against viral diseases such as influenza, pneumococcal diseases, hepatitis, and human papillomavirus [3–6]. This raises the possibility that PLWH can similarly mount suboptimal responses against SARS-CoV-2 infection and vaccination. Furthermore, PLWH have higher SARS-CoV-2 viral loads in nasal swabs than PWOH. HIV-1 infection has been associated with higher rates of hospitalization and increased risk of persistent SARS-CoV-2 replication following infection than observed in PWOH [7,8].

In this review, we focus on the humoral immune response to SARS-CoV-2 infection and vaccination in PLWH and define questions that remain to be addressed. We discuss COVID-19 vaccine efficacy and contrast the quality and magnitude of various mechanisms of antibody-mediated protection in SARS-CoV-2 infection and vaccination in PLWH compared with PWOH. We assess the potential impact of pre-existing immunity against endemic **human coronaviruses (hCoVs)** on SARS-CoV-2 responses in PLWH. We also highlight the impact of prolonged SARS-CoV-2

Highlights

People living with HIV-1 (PLWH) on antiretroviral treatment (ART) present with delayed infection- and vaccine-induced humoral responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) compared with people without HIV-1 (PWOH). However, they eventually reach titers equivalent to those of PWOH.

Differential coordination of SARS-CoV-2 Fc effector functions suggests that antibody responses are qualitatively variable in PLWH, with potential implications for vaccination.

Intrahost diversity is more pronounced in ART-naive PLWH, who may contribute to the divergence of SARS-CoV-2 lineages and/or the emergence of variants of concern.

Existing data on SARS-CoV-2 humoral immunity and intrahost diversity in PLWH supports the need to increase access to ART.

Significance

Given the substantial number of people living with HIV-1 (PLWH), especially in sub-Saharan Africa, understanding the effectiveness of COVID-19 vaccines and antibody responses to SARS-CoV-2 infection and vaccination is essential. Additionally, the impact of pre-existing immunity against endemic human coronaviruses on SARS-CoV-2 responses in PLWH remains underexplored. Prolonged SARS-CoV-2 shedding, and enhanced intrahost diversity observed for PLWH, might be one of the driving forces behind SARS-CoV-2 evolution in Africa and should be further considered, with public health implications worldwide.

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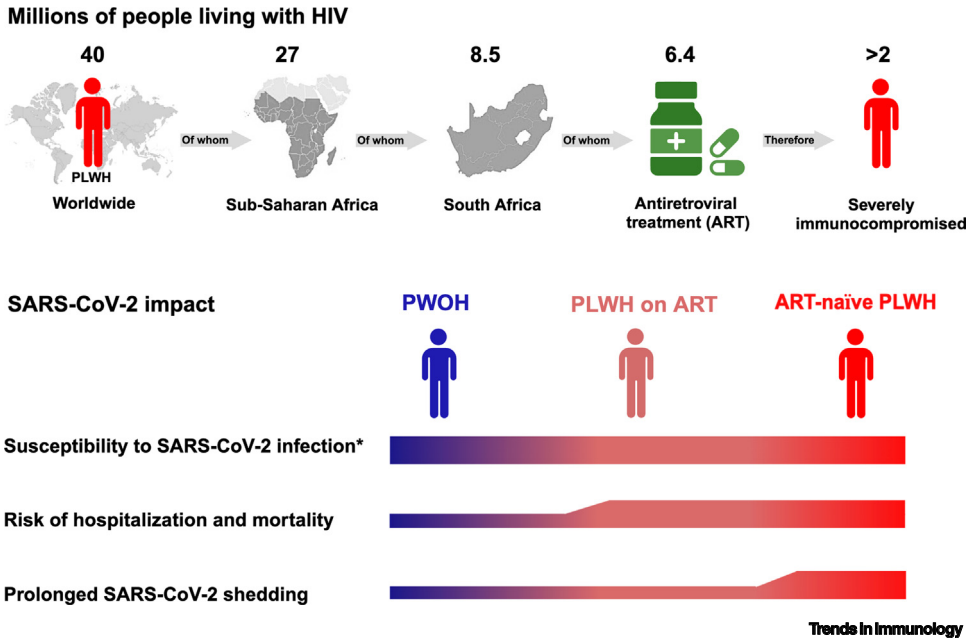

Figure 1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) impact on people living with HIV-1 (PLWH). Of the millions of PLWH worldwide, the majority reside in sub-Saharan Africa[ii]. Despite South Africa providing antiretroviral treatment (ART) to ±75% of PLWH, over 2 million individuals not on ART are likely to be virally unsuppressed and severely immunocompromised[iii]. Susceptibility to SARS-CoV-2 infection in PLWH on ART (pink) and in ART-naive PLWH (red) has been comparable to that in people without HIV-1 (PWOH) [9–12] (blue) (*susceptibility in PLWH has increased with emerging SARS-CoV-2 variants of concern [13]). PLWH are at an increased risk of SARS-CoV-2 hospitalization and mortality irrespective of access to ART [8,14–16]. Prolonged SARS-CoV-2 shedding is most pronounced in ART-naive PLWH [7,20–23]. This figure was created using BioRender.com.

infection in PLWH, including increased intrahost SARS-CoV-2 diversity. Specifically, because prolonged infection has been shown to result in high intrahost diversity in PLWH, we contrast this with viral diversity observed in other immunocompromised individuals. Finally, we assess the potential implications of impaired immune responses, prolonged viral shedding, and intrahost diversity on SARS-CoV-2 evolution in Africa, an issue that has global implications for the continued emergence of new variants of the virus.

The impact of HIV-1 coinfection on SARS-CoV-2 susceptibility and clinical progression

As the SARS-CoV-2 epidemic spread globally, there was concern that PLWH would experience a high level of morbidity and mortality due to COVID-19. While the potential impact of co-infection with HIV-1 was perhaps not as dire as had been predicted, PLWH experienced different susceptibility and disease progression compared with PWOH. During the initial phases of the COVID-19 pandemic, HIV-1 infection was not associated with increased susceptibility to SARS-CoV-2 infection globally and in South Africa [9–12]. However, during the **Omicron** wave in South Africa, PLWH had a 3.2-times higher probability of testing positive for SARS-CoV-2, which was more pronounced in people with lower $CD4^+$ T cell counts, indicative of immune compromise [13]. This is likely the result of a combination of suboptimal immunity in PLWH (described below) with the much greater immune escape capacity and replicative fitness of the Omicron **variant of concern (VOC)** compared with variants circulating earlier in the pandemic, although this remains to be directly demonstrated. Whether PLWH will be at increased risk of infection from newly emerging variants will need to be tracked in the future.

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While susceptibility to infection differed by variant, several studies showed an increased risk of SARS-CoV-2 hospitalizations and mortality in PLWH relative to PWOH throughout the pandemic (Figure 1) [14–16]. This risk of severe COVID-19 disease was heightened in PLWH with high HIV-1 viral loads and low $CD4^+$ T cell counts <200 cells/μl, as well as in individuals who were not on ART [14–16]. This association between HIV-1 infection and SARS-CoV-2 severity has been validated by large population studies in multiple geographic regions with diverse socioeconomic statuses. Of 378 248 COVID-19 diagnoses in the New York State, the rates of COVID-19 hospitalizations were higher in PLWH than in PWOH [17]. In the UK, among 14 882 COVID-19 related deaths, the risk of COVID-19 mortality was elevated in PLWH [18]. Similarly, in South Africa, HIV-1 infection was associated with a 2.14-times higher COVID-19 mortality than PWOH [8]. Among PLWH, male sex, age 45–75 years, and presenting with other comorbidities such as hypertension, diabetes, cancer, tuberculosis, or chronic kidney disease raised the odds of COVID-19 mortality [19]. In addition, there is considerable evidence of prolonged SARS-CoV-2 shedding in individuals with advanced HIV-1 infection [20–23] (described below), with consequences for both the individual and the global population.

Efficacy of COVID-19 vaccination in PLWH

Since poorer vaccine efficacy has been reported for several viral vaccines in PLWH, it was crucial to monitor the efficacy and immunogenicity of COVID-19 vaccines in this population. However, PLWH were often excluded from trials of newly developed vaccines for safety reasons. Therefore, the efficacy of SARS-CoV-2 vaccines in PLWH is less well understood than in the general population, with divergent conclusions that vary by vaccine platform. The Phase 2/3 **BNT162b2 vaccine** trial (ClinicalTrials.gov number NCT04368728)[iv] had too few PLWH enrolled to report on efficacy in this group of individuals [24]. For the Phase 2 trial **NVX-2373 vaccine** (NCT04533399)[v], efficacy among PWOH was 60%, but this was reduced to 49.4% on the inclusion of PLWH [25]. Similarly, in a Phase 3 trial, a single dose of **Ad26.COV2.S vaccine** (NCT04505722)[vi] demonstrated effectiveness against severe COVID-19 and related mortality in the general population (52.9%) but had a lower efficacy in PLWH (23.5%) [26]. However, in another Phase 3 trial (NCT04838795)[vii] of healthcare workers in South Africa, Ad26.COV2.S vaccine effectiveness was comparable in individuals living with or without HIV-1, perhaps because of enhanced awareness of the benefits of ART in this profession [27]. While several immunogenicity studies (discussed below) have been conducted for the **ChAdOx1 nCoV-19 vaccine** in PLWH, no direct impact of HIV-1 infection on efficacy has been reported. Of the few trials that included PLWH [25–27], individuals with advanced HIV-1 infection were excluded for safety reasons. Due to high levels of **hybrid immunity**, addressing whether vaccines (alone) are efficacious in ART-naive PLWH, and those with advanced AIDS, has become nearly impossible now. Therefore, this is a knowledge gap that may not be filled, should retrospective samples not exist.

Binding and neutralizing responses to SARS-CoV-2 infection and vaccination are impaired in PLWH

Many studies comparing immune responses between PLWH and PWOH in SARS-CoV-2 infection or vaccination have primarily focused on IgG binding and neutralization responses, which are crucial for protection and are relatively easy to measure in a standardized way. Several cohorts of PLWH on ART have shown infection-induced SARS-CoV-2-specific IgG titers in serum and neutralizing responses similar to those of convalescent COVID-19 patients without HIV-1 infection (Figure 2, Key figure), in both **pseudovirus** and live virus neutralization assays [28–31]. Additionally, similar kinetics across 0–8 weeks post-symptom onset to peak-concentration IgM and IgG binding responses during acute SARS-CoV-2 infection in ART-controlled PLWH and PWOH have also been reported [29]. However, there are also reports of delayed neutralization of SARS-CoV2 in PLWH on ART [28]. This was true of **D614G** infection but not following **Beta**

Glossary

Ad26.COV2.S vaccine: recombinant, replication-incompetent human adenovirus type 26 vector vaccine encoding full-length spike.
Antibody-dependent cellular cytotoxicity (ADCC): the ability of antibodies to mediate cell killing.
Antibody-dependent cellular phagocytosis (ADCP): the ability of antibodies to mediate cell engulfment.
Antibody-dependent cellular trogocytosis (ADCT): the ability of antibodies to mediate membrane nibbling.
Antibody-dependent complement deposition (ADCD): the ability of antibodies to bind complement and mediate cell killing.
Antibody escape mutations: mutations that develop in the viral coat protein, such as the SARS-CoV-2 spike, as a consequence of immune pressure, and which reduce the ability of antibodies to bind and/or neutralize viruses.
Antiretroviral treatment (ART): a combination of HIV-1 drugs to suppress the replication of virus and improve immune system function.
Back-boosted antibodies: increase in antibody titers towards antigens encountered previously.
Beta: the SARS-CoV2 Beta VOC contained three mutations in the spike protein that resulted in immune evasion.
BNT162b2 vaccine: Pfizer-BioNTech mRNA COVID-19 vaccine.
ChAdOx1 nCoV-19 vaccine: replication-deficient chimpanzee adenoviral vector vaccine against SARS-CoV-2.
D614G: spike mutation at residue 614 that increased SARS-CoV-2 fitness and became fixed in circulating viral populations.
Human coronaviruses (hCoVs): cause mild to moderate upper-respiratory tract illnesses, like the common cold.
Hybrid immunity: occurs through a combination of infection and vaccination, in either order.
Intrahost evolution: viral evolution occurring within an infected individual, often as a consequence of host immune pressure.
mRNA-1273: Moderna mRNA COVID-19 vaccine.
NVX-2373 vaccine: NVX-CoV2373 is a protein-based nanoparticle vaccine targeting SARS-CoV-2.

infection, which suggests that the kinetics of humoral immunity may vary by the infecting variant [28]. COVID-19 severity also influences the magnitude of the humoral response in both PLWH and PWOH [30]. Specifically, severe COVID-19 induces comparable binding IgG titers in serum between PLWH and PWOH while symptomatic non-hospitalized disease results in a lower magnitude of binding IgG titers in the serum of PLWH compared with PWOH, measured by binding antibody multiplex assays [32]. Also, in ART-naive or HIV-1 viremic PLWH with low $CD4^+$ T cell counts of <200 cells/μl, IgG binding and neutralizing antibody titers are substantially reduced following SARS-CoV-2 infection compared with PLWH on ART, suggesting that immune reconstitution through the use of ART helps to improve responses to SARS-CoV-2 [28,33,34]. A related key question is what happens to antibody responses in PLWH who initiate ART. In individuals with advanced HIV-1 infection who initiated ART treatment (but prior to complete HIV-1 suppression), SARS-CoV-2 clearance was achieved with the emergence of neutralizing responses [35]. However, given that, in this study, neutralization titers were highly variable at enrollment [ranging in titers from below 20 to over 3000 NT_{50} (50% neutralization)] [35], whether initial suboptimal responses could eventually reach similar titers, as reported in ART-treated individuals (see below) [28], is unknown. Additional studies in the population would be informative.

In the context of vaccine-induced humoral immunity, several studies have reported similar binding and neutralizing responses between PLWH on ART and PWOH following SARS-CoV2 BNT162b2, **mRNA-1273**, Ad26.COV2.S, and ChAdOx1 nCoV-19 vaccination [26,33,36–40]. Our research group observed delayed IgG binding to vaccine antigen 28 days after the first dose of ChAdOx1 nCoV-19 in South Africa. However, after the second dose, similar to other studies [39,41], PLWH achieved equivalent or higher IgG binding than PWOH at 6 months post-vaccination, suggesting that antibody titers were not compromised in this group [28]. Others also demonstrated higher SARS-CoV-2 spike protein binding antibody titers in PLWH compared with PWOH with each dose of ChAdOx1 nCoV-19 (NCT04444674[viii] and Pan African Clinical Trials Registry PACTR202006922165132[ix]) [39]. Further studies are needed to validate and provide a mechanism for this surprising observation of higher titers in some PLWH in the long-term relative to PWOH, potentially due to higher SARS-CoV-2 viral loads.

In addition, in terms of hybrid immunity, PLWH (with controlled HIV-1 infection) developed equivalent binding or neutralizing antibody responses compared with PWOH when boosted with either the Ad26.COV2.S or the BNT162.b2 vaccine, suggesting that this population was well protected by vaccination [33,42]. However, although participant numbers were limited, this study also showed that individuals with $CD4^+$ T cell counts <200 cells/μl (representative of a compromised immune system) displayed low or no B and T cell responses to spike prior to being boosted. This suggested that, in virally unsuppressed PLWH (those not on effective ART), SARS-CoV-2-specific responses might be significantly less durable than in PWOH, even in the context of prior infection, meaning this subgroup may require further vaccine boosters to enhance responses [42,43].

Overall, while there were initial delays in vaccine-elicited binding and neutralizing antibody responses in PLWH compared with PWOH, these delays did not compromise the ability of PLWH to reach comparable peak titers at later time points [28]. These findings for PLWH are in stark contrast to what has been seen in other immunocompromised individuals, who mount significantly reduced antibody responses compared with healthy individuals or do not seroconvert following SARS-CoV-2 vaccination [44–46]. The differences in SARS-CoV-2 responses between PLWH and PWOH appear to be largely influenced by the immune competence of the PLWH included. Therefore, although there remains a paucity of cohorts that include ART-naive PLWH, these data nonetheless support the need to increase ART access for improved SARS-CoV-2 vaccine-elicited and infection-induced protection mediated by binding and neutralization activity.

Omicron: the SARS-CoV2 Omicron VOC accumulated more than 30 spike mutations resulting in immune evasion and enhanced transmissibility.
People living with HIV-1 (PLWH): individuals diagnosed with HIV-1 infection, which attacks their immune systems and can progress to AIDS.
Pseudovirus: recombinant virus with the core or backbone (e.g., lentivirus) and surface proteins (e.g., SARS-CoV-2 spike) derived from different viruses; used to measure neutralization titers.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): the causative agent of COVID-19.
Variants of concern (VOCs): highly mutated SARS-CoV-2 variants with detrimental change in clinical severity or change in COVID-19 epidemiology or significant decrease in vaccine effectiveness.
Variants of interest (VOIs): mutated SARS-CoV-2 variants with predicted impact on virus characteristics (e.g., transmissibility, virulence, antibody evasion, susceptibility to therapeutics, detectability); have a growth advantage over other circulating variants in more than one World Health Organization region.

Key figure

Humoral responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and vaccination in people living with HIV-1 (PLWH)

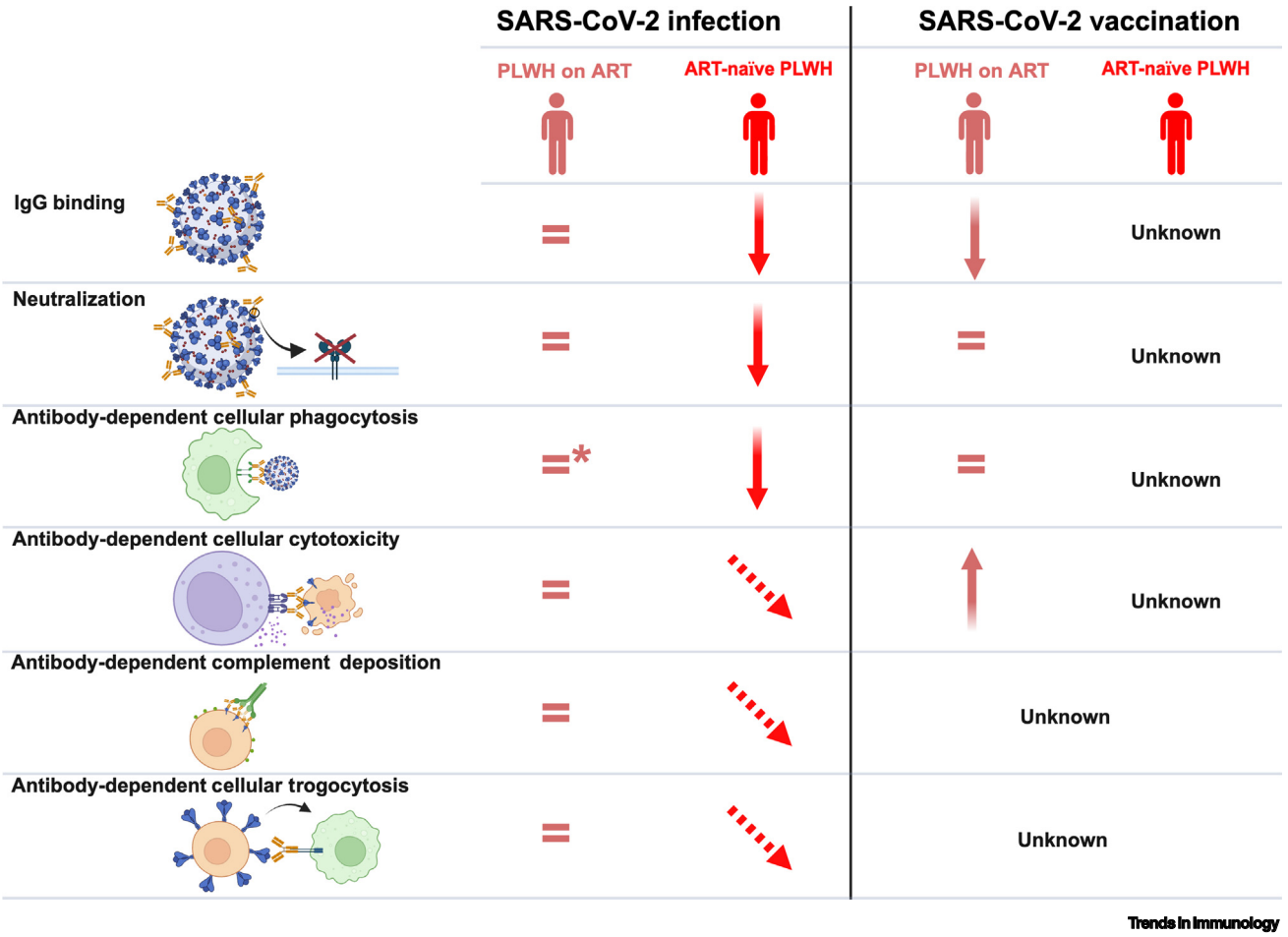

Figure 2. Compared with people without HIV-1 (PWOH), PLWH on antiretroviral treatment (ART) (pink) have comparable (=) antibody responses following SARS-CoV-2 infection [28–31]. *Coronavirus disease 2019 (COVID-19) symptomatic or hospitalized PLWH on ART have been shown to display significantly lower antibody-dependent cellular phagocytosis (ADCP) compared with PWOH [32]. Compared with PLWH on ART, ART-naive PLWH (red) have significantly lower binding, neutralizing, and ADCP responses, indicated by the downward arrow [28]. Antibody-dependent cellular cytotoxicity (ADCC), complement deposition (ADCD), and cellular trogocytosis (ADCT) trend lower (diagonal arrow) in ART-naive PLWH [28]. Vaccine-induced binding is initially lower in PLWH on ART, but this does not affect neutralizing and ADCP responses, which are similar to PWOH and to ADCC responses, and higher than in PWOH [28]. There have been no reports on vaccine-induced antibody responses in ART-naive PLWH; also, ADCD and ADCT have not been studied in PLWH on ART. Therefore, the characteristics of these responses in this immunocompromised population remain unknown. This figure was created using BioRender.com.

SARS-CoV-2 Fc effector functions are differentially regulated in PLWH

It is now well established that, beyond neutralization, binding antibody titers alone correlate with protection from SARS-CoV-2 infection and with delayed progression to severe COVID-19 disease in individuals without HIV-1 infection [47,48]. In addition, the ability of cells to recruit cytotoxic functions from other immune cells by binding to Fc receptors or complement proteins (known as Fc effector functions) has been correlated with protection following SARS-CoV-2

vaccination and with decreased severity and mortality in patients without HIV-1 infection [49–54]. Moreover, Fc effector functions are more durable and more resilient in the face of mutated VOCs compared with neutralizing antibodies against SARS-CoV-2, which often lose activity against VOCs in neutralization assays [55–58]. Fc effector functions are required for monoclonal antibodies to optimally protect against SARS-CoV-2 infection in hamster models [59]. These functions, which include **antibody-dependent cellular phagocytosis (ADCP)**, **antibody-dependent cellular cytotoxicity (ADCC)**, **antibody-dependent complement deposition (ADCD)**, and **antibody-dependent cellular trogocytosis (ADCT)**, have been examined in PWOH, showing robust elicitation in response to all vaccine modalities [51,52,60]. However, little is known about these responses in PLWH. Furthermore, these Fc-mediated functions may have an important role in cross-reacting pre-existing immunity from endemic hCoVs to SARS-CoV-2 (as discussed in Box 1).

Of note, we previously showed that PLWH on ART elicited a robust Fc-mediated response, including *in vitro* ADCC, ADCD, ADCT, and ADCP assays after SARS-CoV-2 infection, with magnitudes being similar to those of PWOH (Figure 2) [28]. Similarly, equivalent response rates and ADCP in a multinational (USA and Peru) cohort of PWOH and ART-suppressed PLWH were reported using culture-based functional assays [32]. ADCP responses in these individuals were robust, considering that the IgG titers were lower than those of the few hospitalized PLWH included in the study [32]. Thus, the ability to elicit ADCP was sustained, irrespective of binding antibody titers and disease severity, suggesting that ADCP was not directly related to these features but, rather, relied on the quality of the antibody response. Of note, these participants had either asymptomatic or symptomatic SARS-CoV-2 infection not requiring hospitalization [32]; however, we also observed comparable ADCP between hospitalized PWOH and PLWH irrespective of whether these individuals were infected by the D614G or the Beta variant [28], suggesting that severity of infection was not a major contributor to this observation. In D614G-infected individuals, however, PLWH had significantly delayed ADCP over 1 week post infection compared with PWOH [28]. The precise clinical significance of this delay in the acute ADCP response remains to be defined; however, given the importance of ADCP in the acute stages of other viral diseases such as HIV-1 infection [61], this delay may have an impact on SARS-

Box 1. Pre-existing humoral immunity against endemic hCoVs

Antibody immunity against endemic hCoVs is short lived, resulting in widespread annual mild reinfections [81]. The impact of pre-existing immunity to endemic hCoVs such as *Betacoronavirus* HKU1 and OC43 on SARS-CoV-2 antibody responses remains uncertain. Several research groups showed that SARS-CoV-2 infections **back-boosted antibodies** that were elicited by prior endemic hCoV infection, and that bound with strong affinity to the spike of endemic hCoVs, resulting in poorer SARS-CoV-2-specific responses than individuals without prior infection by endemic hCoVs [82,83]. These studies demonstrated an association between IgG titers to endemic hCoVs and COVID-19 severity (measured by ELISA) [82,83]. Conversely, others have shown that, while the protection conferred by cross-reacting endemic hCoV immunity is not sufficient to block SARS-CoV-2 infection in neutralization assays, it has been associated with reduced disease severity and asymptomatic COVID-19 in PWOH [84–86]. In a recent study, individuals with high pre-existing serum IgG against hCoVs reported significantly fewer disease symptoms following SARS-CoV-2 infection [84], and previous studies suggested that COVID-19 mortality was reduced in individuals with pre-existing immunity to hCoVs [85,86]. Much of the described impact on these improved outcomes has been on binding antibodies rather than on neutralizing antibodies; often, these specifically target the S2 region of the SARS-CoV-2 spike, which is highly conserved between OC43 and SARS-CoV-2 [87]. S2-specific antibodies can potently engage Fc receptors, which is important because these functions are associated with reduced mortality [88,89]. However, whether this extends to PLWH is unknown. Given that PLWH have higher susceptibility to severe respiratory disease and perhaps increased exposure to endemic hCoVs, this may be especially relevant as a concern for the achievement of optimal SARS-CoV-2 humoral responses in this population. In a cohort of PLWH in Lesotho, South Africa, higher pre-existing immunity to endemic hCoVs was associated with higher antibody responses to SARS-CoV-2 infection, but a protective effect was not observed [90]. Therefore, further studies may shed light on whether pre-existing immunity to endemic hCoVs in PLWH reduces or increases the risk of severe COVID-19 in these individuals.

CoV-2 infection kinetics, which in turn may be of clinical relevance for these patients. Of note, ART-naive PLWH had significantly lower ADCP values than PLWH on ART, illustrating that Fc effector function was also compromised in this population [28].

Furthermore, despite delays in some responses, PLWH triggered a more coordinated Fc effector response compared with PWOH following SARS-CoV-2 infection in cell-based functional assays using serum [28]. Increased coordination between responses has been associated with COVID-19 convalescence in humans and in vaccinated nonhuman primates (NHPs) using the same *in vitro* assays, suggesting that PLWH may utilize these functions in mechanistically different manners [52,62]. Given that antibody Fc effector functions contribute to protection, it is important that we leverage these responses through vaccination, especially for vulnerable populations. These populations include individuals with other immune perturbations in which Fc effector function has not been evaluated, such as individuals with systemic lupus erythematosus or rheumatoid arthritis. However, given that Fc glycosylation (as measured by glycan sequencing) is a major modulator of Fc effector responses, and is directly impacted by inflammatory diseases compared with healthy individuals [63], these functions are likely to be impaired or differentially regulated in other immunocompromised individuals. Therefore, the clinical impact of these outcomes is something that should be monitored.

While again not extensively evaluated in PLWH, SARS-CoV-2 vaccine-induced Fc-mediated functions such as ADCC (measured via FcγRIIIa-signaling assays) have been durable, lasting 6 months and exceeding what has been observed in PWOH after ChAdOx1 nCoV-19 vaccination [28,39]. This highlights that ADCC may be an important mechanism for protection against SARS-CoV-2. However, in this study, ADCC was not uniform for all Fc effector functions where ADCP was significantly lower in PLWH compared with PWOH [28]. Therefore, immune perturbation from HIV-1 co-infection may enhance some Fc effector functions but compromise others, likely as a result of specific isotype elicitation or from differential Fc glycosylation, which has been suggested but remains to be investigated [63]. While our studies examined vaccine-elicited Fc effector functions in PLWH that were well controlled on ART, another study showed that, 4 weeks after the second dose of one of the SARS-CoV-2 mRNA vaccines, individuals with $CD4^+$ T cell counts <250 cells/μl exhibited less antibody ADCC activity than antibodies from individuals with $CD4^+$ T cell counts >250 cells/μl, as evidenced in function cell-based assays [41]. However, these differences were not observed after the third dose, indicating that boosting in severely immunocompromised individuals can restore ADCC values that are comparable with those of PWOH; this suggests that PLWH may be at an early disadvantage, but that this effect may be short lived and temporary [41]. This highlights the importance of investigating the kinetics of Fc effector responses against SARS-CoV-2 in PLWH, as these provide insights into the mechanisms required for immunity and vaccine efficacy in this population, as well as the strategies that may be required to differentially boost these responses.

Prolonged SARS-CoV-2 infection and virus shedding in immunocompromised individuals

The emergence of SARS-CoV-2 VOCs with increased replicative fitness, differential preference for cell entry, alternate tropism, increased antibody neutralization escape, and consequently enhanced transmissibility poses challenges to viral surveillance, diagnostic reliability, and vaccine effectiveness [64]. Increasing evidence suggests that SARS-CoV-2 genetic variability occurs more rapidly and frequently in immunocompromised individuals through the process of **intrahost evolution** [65–67]. Coupled with the inability to clear infection rapidly, immunocompromised individuals may represent a 'source' for rapid and extended viral evolution (Figure 3).

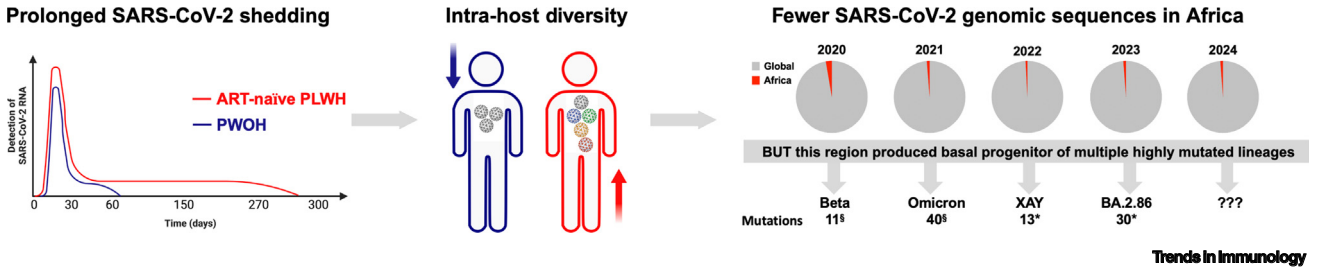

Figure 3. Consequences of persistent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in people living with HIV-1 (PLWH). The longest shedding period reported in people without HIV-1 (PWOH) (blue) was 60 days [68], whereas in advanced HIV-1 infection (PLWH; red) the longest period reported was ±270 days, as indicated by the graph [23]. PLWH have higher SARS-CoV-2 viral loads on infection than PWOH [7], and prolonged shedding results in greater intrahost diversity in these individuals [20–23,67]. These extended shedding periods and increased mutational rates in PLWH may have contributed to the significant evolution of SARS-CoV-2 observed in Africa [79,80]. Despite fewer SARS-CoV-2 genomic sequences from 2020 to 2024, two of five variants of concern (VOCs), Beta (2020) and Omicron (2021), were identified first in Africa [64,80]. In addition, basal progenitors of multiple highly mutated lineages, such as XAY (2022) and BA.2.86 (2023), are more closely related to sequences from Africa [75–78]. The number of mutations relative to ancestral § and Omicron* variants are shown[x] [64,77,80]. This figure was created using BioRender.com.

One high-resolution study conducted in the UK investigated the frequency of prolonged infections in a household-based surveillance study with individuals devoid of comorbidities, representing the general population; the data showed that 0.1–0.5% of infections could become persistent for at least 60 days [68]. This suggested that this effect was not limited to immunocompromised individuals. Moreover, this study was intriguing in that the median age of individuals with persistent infections was higher (by 6–21 years) for all variants (Alpha to Omicron BA.1) compared with individuals without prolonged shedding, suggesting that prolonged infection in PWOH might be higher in older individuals [68]. Thus, even in PWOH, immune suppression, in this case due to older age, might be a risk for persistent infection. However, in the context of individuals hospitalized for severe COVID-19, viral shedding occurs for longer periods in immunocompromised individuals than in immunocompetent patients [7,67,69]. Poor adherence to ART may progress to advanced HIV-1 infection, which is characterized by high HIV-1 viral loads, low $CD4^+$ T cell counts, and dysregulated B cell responses [70]. Immune dysfunction linked to advanced HIV-1 infection is associated with an inability to clear SARS-CoV-2 for up to 9 months post-infection [23]. Moreover, prolonged SARS-CoV-2 infection, which provides a longer period for the accumulation of viral mutations, has been well documented for PLWH but is most pronounced in individuals with advanced HIV-1 infection (as well as in patients with conditions requiring immunosuppressive medications and in individuals with B cell deficiencies), suggesting that these patients may represent a source of highly mutated SARS-CoV-2 viruses [23,67]. These mutations do not just reflect changes in viral replicative fitness, but importantly, have also been detected in antigenic regions, including the N-terminal domain (NTD) and receptor binding domain (RBD) of SARS-CoV-2. Notably, prior to the emergence of the Beta, Gamma, and Delta variants, characterized by the E484K and L452R mutations, retrospective whole-genome sequencing detected these mutations in multiple case studies of PLWH with prolonged SARS-CoV-2 infection that were not detected in PWOH [20,67]. These studies provide direct evidence of the emergence of **antibody escape mutations**, including those in pre- and post-Omicron variants. What remains largely unknown is the mechanism by which the humoral antibody response impacts SARS-CoV-2 intrahost diversity and whether this viral diversity in turn has negative or positive consequences for subsequent antibody responses.

Evolution of SARS-CoV-2 in Africa

South Africa had the highest SARS-CoV-2 infection rate on the African continent. While this may have been largely linked to relatively higher testing efforts, the region forms a focal point for SARS-CoV-2 genomic and immunological surveillance in Africa [71]. While all five VOCs were detected

in other African countries, intriguing regional differences were observed; for example, the predominance of Alpha or Eta, rather than Beta, in North and West African countries [72–74]. Early in the pandemic, while most introductions of SARS-CoV-2 occurred via Europe or Asia, several novel African lineages arose; however, these lineages only contained synonymous changes in the spike gene [73]. In the second half of 2020, following convergent evolution of SARS-CoV-2 in multiple geographic locations, associated with functional changes especially in the spike gene, the Beta variant, which was the most neutralization-resistant pre-Omicron VOC, emerged from South Africa [64]. This variant displayed seven spike gene amino acid substitutions that were confirmed to mediate neutralization resistance from both vaccine and infection-induced immunity, as evidenced by pseudovirus and live virus neutralization assays [49–51]. This was not the only mutated pre-Omicron variant that emerged from Africa; others included the A.VOI.V2, C.16, and C.1.2 lineages [75,76]. During the first year of the SARS-CoV-2 pandemic, prior to the emergence of VOCs or **variants of interest (VOIs)**, SARS-CoV-2 evolution displayed a standard molecular clock-like fashion, indicative of a predictable evolutionary rate [73]. However, the emergence of VOCs and VOIs represented short bursts of increased evolution, which supports the theory of these variants emerging through prolonged SARS-CoV-2 infection [76].

Most notable has been the emergence of the highly mutated Omicron (and its sublineages) and, recently, BA.2.86 (ancestor of the currently dominant JN.1 lineage). Both had >30 mutations away from the previously dominant variants and for both the earliest collected samples originated from Africa, despite significantly reduced testing and sequencing efforts [77]. Given the strong selection pressure observed across the 11 genes in Omicron, a substantial role of adaptive evolution in its emergence is likely; this has provided support for the accumulation of these mutations in an instance of prolonged SARS-CoV-2 infection [78].

While factors such as travel patterns, vaccination coverage, and immunity from prior infection certainly contributed to geographical differences in SARS-CoV-2 evolution, Africa's heavy HIV-1 burden has likely contributed to the identification of highly divergent SARS-CoV-2 lineages. The hypothesis that PLWH may represent a distinct reservoir for VOCs remains valid (Figure 3) [79,80]; however, data showing the direct coevolution of SARS-CoV-2 and the host humoral immune response in this immunocompromised population, in either acute or prolonged SARS-CoV-2 infection, is a key outstanding question. Regardless, the likelihood of continued emergence of highly divergent SARS-CoV-2 lineages from Africa and other continents means that continual updates to SARS-CoV-2 vaccines will be required.

Concluding remarks

Although PLWH may have delayed or dampened initial humoral responses to SARS-CoV-2 infection or vaccination, the quality of these lower-titer responses in many cases reaches equivalent or even higher titers than PWOH [28]. Furthermore, there is some evidence that the humoral responses in PLWH are qualitatively different with increased coordination between responses, which may be of clinical benefit [28]. If this improved coordination in PLWH is a generalizable observation, a higher quality of responses might be leveraged in future vaccines (see Outstanding questions). PLWH, and specifically those with unsuppressed HIV-1 infection, are at an increased risk for prolonged SARS-CoV-2 viral shedding [7,20–23]. The ongoing shedding in PLWH represents a risk for the individual, but also for the community, because persistent infection is associated with the rapid accumulation of SARS-CoV-2 mutations, which may have contributed or may contribute to the emergence of VOCs [20–22,67,79,80]. To reduce the public health impact of persistent infection and associated emergence of VOCs and inform vaccine implementation in PLWH, a deeper understanding of the immune responses to SARS-CoV-2 infection and vaccination in these individuals is needed.

Outstanding questions

What factors contribute to varying titers of vaccine-induced neutralizing antibodies in PLWH who have recently initiated ART and how can we alter vaccination strategies to ensure high titers in all individuals? Because high-titer vaccine-induced antibody responses limit viral propagation and subsequent transmission, understanding of the inconsistent induction of strong antibody responses in PLWH is key.

In PLWH, delays have been reported in the development of ADCP during acute SARS-CoV-2 infection. Does this have a clinical impact, and how could vaccine strategies mitigate this?

PLWH have a more coordinated immune response to SARS-CoV-2 infection than PWOH. How can we leverage this to enhance SARS-CoV-2 vaccine-induced immune responses in PWOH?

What impact does humoral immunity have on intrahost SARS-CoV-2 diversity in immunocompromised PLWH? Conversely, does this SARS-CoV-2 diversity drive humoral immunity along a particular path? Could this be another contributing factor to why the expected impact of SARS-CoV-2 infection in PLWH has not come to fruition?

PLWH are at higher risk of long-term shedding than PWOH, and millions of PLWH are unable to access ART globally and are thus immunocompromised. Is the emergence of highly mutated SARS-CoV-2 lineages more prevalent in countries with high HIV-1 infection incidence?

In ART-naive PLWH, is SARS-CoV-2 vaccine-induced immunity suppressed until ART is initiated? On ART initiation, do these antibody titers then reach comparable amounts? This has implications for the hypothesis that prolonged infection in ART-naive PLWH drives the emergence of SARS-CoV-2 variants of concern. Could this suggest that widespread ART access might reduce the risk of VOC emergence?

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Declaration of interests

The authors declare no competing interests.

Resources

[i]https://covid19.who.int

[ii]www.unaids.org/en/resources/documents/2023/global-aids-update-2023

[iii]https://apps.who.int/gho/data/view.main.23300?lang=en

[iv]https://clinicaltrials.gov/study/NCT04368728?cond=NCT04368728&rank=1

[v]https://clinicaltrials.gov/study/NCT04533399?cond=NCT04533399&rank=1

[vi]https://clinicaltrials.gov/study/NCT04505722?cond=NCT04505722&rank=1

[vii]https://clinicaltrials.gov/study/NCT04838795?cond=NCT04838795&rank=1

[viii]https://clinicaltrials.gov/study/NCT04838795?cond=NCT04444674&rank=1

[ix]https://trialsearch.who.int/Trial2.aspx?TrialID=PACTR202006922165132

[x]https://cov-lineages.org/resources/pangolin.html

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