

Topics in Antiviral Medicine™

A publication of the IAS–USA

Invited Reviews

COVID-19 Treatments: Current Options and Therapies Under Investigation **CME**

Skye Opsteen, MS; Nathaniel Erdmann, MD, PhD

Acute COVID-19 • Antiviral Therapy • Long COVID • New Drugs • Pathogenesis • Postviral Syndromes • SARS-CoV-2

2026 Update on Routine and Special Vaccinations in People With HIV **CME**

Hillary A. Dunlevy, MD, MPH; Steven C. Johnson, MD

COVID-19 • Hepatitis A • Hepatitis B • Herpes Zoster • Human Papillomavirus • Influenza • Measles, Mumps, and Rubella • Meningococcal Disease • Mpox • Pneumococcal Disease • Respiratory Syncytial Virus • Travel Vaccines • Vaccine Hesitancy

Drug-Drug Interactions, Dosing, Formulations, and Other Pharmacologic Issues in HIV Management: A Week on Consultation With Your HIV Clinical Pharmacologist **CME**

David M. Burger, PharmD, PhD

Drug-Drug Interactions • Pediatric HIV • Pharmacokinetics • Pharmacology • Therapeutic Drugs

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Invited Reviews

- COVID-19 Treatments: Current Options and Therapies Under Investigation **CME** 575

Skye Opsteen, MS; Nathaniel Erdmann, MD, PhD

- 2026 Update on Routine and Special Vaccinations in People With HIV **CME** 585

Hillary A. Dunlevy, MD, MPH; Steven C. Johnson, MD

- Drug-Drug Interactions, Dosing, Formulations, and Other Pharmacologic Issues in HIV Management: A Week on Consultation With Your HIV Clinical Pharmacologist **CME** 596

David M. Burger, PharmD, PhD

Announcements

- About This Issue 574
- Correction to 2025 Update of the Drug Resistance Mutations in HIV-1 574
- Guidelines for Authors and Contributors 603

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Learning Objectives

On completion of this activity, which includes 3 articles covering important information on COVID-19 treatment, vaccination recommendations for people with HIV, and pharmacologic management of antiretroviral therapy for people with HIV, the learner will be able to:

- Describe current treatment recommendations for acute COVID-19 and evaluate emerging therapeutic approaches for long COVID
- Outline current vaccination recommendations for people with HIV, taking into consideration immune status, vaccine timing, and contraindications
- Describe pharmacology principles to optimize antiretroviral dosing and formulations, manage drug-drug interactions, and minimize toxic effects and resistance in people with HIV

This enduring material is designed for physicians who are actively involved in the medical care of people with HIV and other viral infections.

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Correction

Correction to: Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. 2025 update of the drug resistance mutations in HIV-1. *Top Antivir Med.* 2025;33(2):457-473. <https://www.iasusa.org/wp-content/uploads/2025/05/33-2-457.pdf>

From February 26, 2026, through September 18, 2026, a version of the Drug Resistance Mutations **Figure** incorrectly and preliminarily included islatravir in the nonnucleoside reverse transcriptase inhibitor (NNRTI) section. Islatravir is a nucleoside reverse transcriptase translocation inhibitor (NRTTI). The **Figure** has been corrected to remove the preliminary version of islatravir from the NNRTI section. Islatravir and its relative mutations will be added to the appropriate section in a future iteration of the **Figure**.

See also: Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. Current evidence on islatravir drug resistance and implications for future HIV treatment. *Top Antivir Med.* 2026;34(3):527-532. <https://www.iasusa.org/tam-34-1-wensing/>

Invited Review

COVID-19 Treatments: Current Options and Therapies Under Investigation

Skye Opsteen, MS; Nathaniel Erdmann, MD, PhD

University of Alabama at Birmingham

Abstract: *The COVID-19 pandemic has contributed to more than 7 million deaths globally and has triggered a variety of postacute sequelae, now commonly referred to as long COVID, in millions more. Early efforts during the pandemic resulted in several therapies to mitigate the severity and mortality of acute COVID-19. However, despite effective therapies and accumulated immunity through vaccination and natural infection reducing disease severity, COVID-19 continues to contribute to hospitalizations and mortality. Long COVID encompasses several distinct yet overlapping clinical syndromes, and evidence suggests that these manifestations are mediated by numerous underlying mechanisms. There are currently no approved therapies for the treatment of long COVID, driven in part by its heterogeneity in presentation and etiology. This review will outline the current guidelines for treating acute COVID-19 and summarize information on the mechanistic rationale behind various published and ongoing clinical trials investigating potential long COVID therapeutic agents.*

Keywords: antiviral therapy, clinical trials, COVID-19, immune dysregulation, long COVID, new drugs, PASC, pathogenesis, persistent viral reservoirs, postacute sequelae of SARS-CoV-2 infection, postviral syndromes, SARS-CoV-2

Introduction

The COVID-19 pandemic caused by SARS-CoV-2 began in late 2019 and has contributed to more than 7 million deaths globally.¹ Although the introduction of therapeutic agents and accumulated immunity through vaccination and natural infection have reduced the frequency of severe disease, COVID-19 continues to contribute to thousands of hospitalizations and hundreds of deaths globally each week.¹

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Although most individuals infected with SARS-CoV-2 recover fully, current estimates suggest that 4% of children and 10% to 26% of adults develop postacute sequelae of COVID-19 (PASC), also referred to as long COVID.²

The underlying pathophysiology of long COVID remains poorly understood and appears heterogeneous, which has limited progress in identifying therapeutic targets. Consequently, there are currently no approved treatments specific to long COVID, but numerous clinical trials in progress. This review provides an overview of therapeutic agents for acute COVID-19 and summarizes the

Therapeutic agents and accumulated immunity have reduced the frequency of severe disease, but COVID-19 continues to contribute to thousands of hospitalizations and hundreds of deaths globally each week

mechanistic rationale underpinning potential drugs that are currently in clinical development for the treatment of long COVID.

Acute COVID-19

Risk factors for severe COVID-19 include male sex, older age, neutralizing autoantibodies against type I interferons,³ and comorbidities such as obesity, diabetes, and cardiopulmonary disorders. Initial reports on COVID-19 cited the risk of severe disease as high as 50%, which led to urgent efforts exploring potential therapeutic options to reduce disease severity and the likelihood of hospitalization. Within the first year of the pandemic, 3 major therapeutic options, remdesivir, immunoglobulins (monoclonal antibodies, convalescent plasma), and corticosteroids, reduced time to recovery and mortality in

patients hospitalized for COVID-19. Clinical management subsequently evolved to incorporate the routine use of antiviral, corticosteroid, and immunomodulatory treatments including tocilizumab and baricitinib.

Viral-directed therapeutic agents such as antiviral drugs, convalescent plasma, and monoclonal antibodies have been shown to decrease disease progression and consequently, to reduce rates of hospitalization, respiratory failure, and mortality. The first Food and Drug Administration (FDA)-approved antiviral drug for COVID-19 was remdesivir, a nucleoside analogue that inhibits viral RNA-dependent RNA polymerase. Remdesivir received Emergency Use Authorization (EUA) in mid-2020 after it was shown to reduce the time to recovery in adults hospitalized for COVID-19 in numerous clinical trials.⁴

Shortly after remdesivir received FDA approval for individuals with moderate to severe COVID-19, EUAs for convalescent plasma and monoclonal antibodies (bamlanivimab-etesevimab and casirivimab-imdevimab) were issued. Convalescent plasma was quickly identified as a potential therapy, with varying degrees of testing and implementation across the globe. In China, convalescent plasma was used to treat patients hospitalized with COVID-19 early in the pandemic,⁵ leading to randomized clinical trials across various countries including the US. Although some studies showed potential benefit, particularly with high-titer plasma, others observed no impact on disease progression and mortality.⁵ Many of these studies were limited by heterogeneous patient populations, inadequate power, lack of untreated controls, and unaccounted confounding variables, resulting in insufficient evidence to support the routine use of convalescent plasma.⁵

SARS-CoV-2-directed monoclonal antibodies like bamlanivimab-etesevimab and casirivimab-imdevimab demonstrated reductions in hospitalization and mortality due to COVID-19, although their clinical utility has been dramatically reduced with the emergence of newer variants.^{6,7} Remdesivir, convalescent plasma, and monoclonal antibodies all rely on intravenous infusion. Thus, their use has been largely limited to patients already hospitalized with COVID-19 or at high risk for hospitalization who had prompt access to infusion clinics, spurring interest in oral alternatives for use earlier in SARS-CoV-2 infection to prevent hospitalization.

By early 2022, the oral antiviral agents nirmatrelvir/ritonavir and molnupiravir received EUAs for outpatient use. The combination drug comprising the protease inhibitor nirmatrelvir and pharmacokinetic enhancer ritonavir was first tested in symptomatic, unvaccinated, nonhospitalized adults at high risk for disease progression and demonstrated lower rates of hospitalization and death.⁸

Molnupiravir, a nucleoside analogue that promotes deleterious errors during viral replication, demonstrated more modest reductions in hospitalization and mortality rates in similar high-risk populations.⁹ When later assessed in vaccinated, high-risk patients, nirmatrelvir/ritonavir and molnupiravir demonstrated no further reduction in the

A post hoc analysis found that dexamethasone increased mortality in individuals not requiring oxygen supplementation, underscoring the importance of aligning therapy with disease stage

incidence of hospitalization or mortality, which was reported in less than 1% of all participants in these studies, emphasizing the important role of vaccination in reducing disease severity.^{10,11} Although less effective, molnupiravir is an option for patients who are unable to take nirmatrelvir/ritonavir due to its substantial drug-drug interactions with many medications. Remdesivir and nirmatrelvir/ritonavir went on to be approved for use in adults and children, whereas molnupiravir is approved for adult use.

Shortly after remdesivir demonstrated benefit in reducing recovery time, dexamethasone was shown to reduce the mortality rate in those requiring supplemental oxygen or invasive mechanical ventilation.¹² A post hoc analysis found that dexamethasone actually increased mortality in individuals not requiring oxygen supplementation,¹³ underscoring the importance of aligning therapy with disease stage. These findings also demonstrated maximal benefit when corticosteroids were administered at least 1 week after symptom onset, corresponding to the inflammatory phase of COVID-19 disease.

Additional immune modulators such as Janus kinase (JAK) inhibitors (ie, baricitinib) and interleukin (IL)-6 antagonists (ie, tocilizumab, sarilumab) have also shown success in reducing disease progression and mortality rate when used alongside remdesivir, corticosteroids, and respiratory support.^{14,15} Abatacept, a T-cell costimulatory modulator, and infliximab, a tumor necrosis factor (TNF) inhibitor, demonstrated reduced mortality rates, although neither agent shortened time to recovery.¹⁶

Vaccination remains the mainstay in preventing severe infection and death from SARS-CoV-2. In a 2022

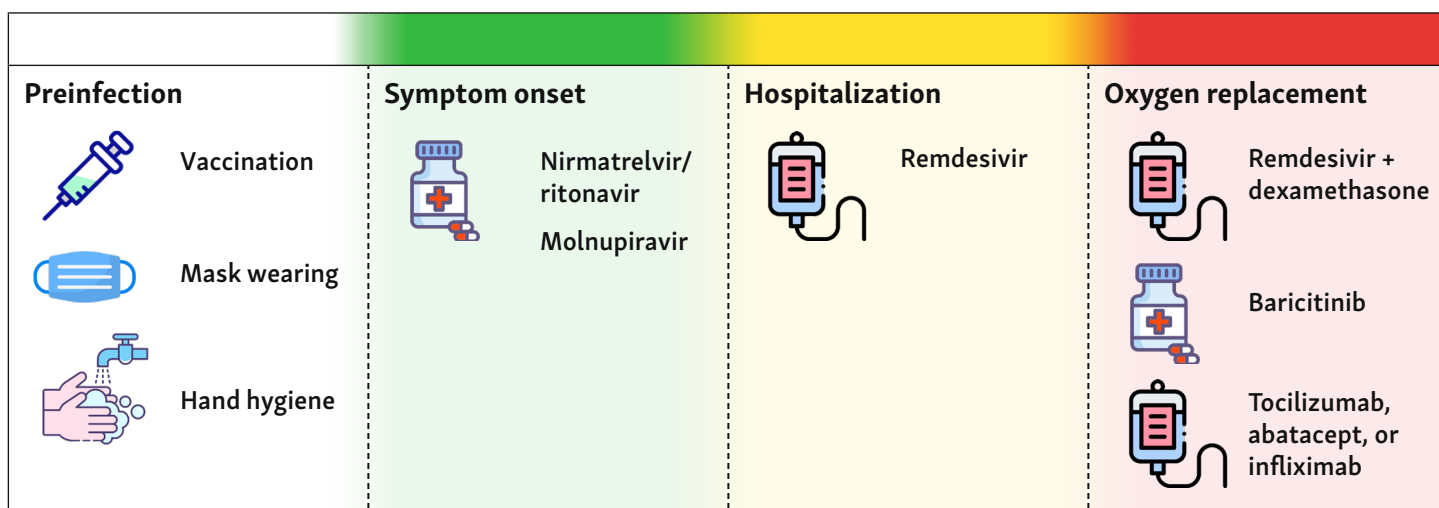


Figure 1. Recommended interventions by stage or severity of COVID-19.

meta-analysis, full vaccination with various platforms (ie, mRNA, viral vector, and protein subunit based) provided strong protection against severe disease, with the greatest benefit attributed to mRNA vaccination. Additionally, mRNA vaccines showed the greatest benefit against variants of concern regarding other vaccination methods.¹⁷ In addition to vaccination, other prevention measures can be utilized to mitigate risk of infection. Recently, ensitrelvir, a SARS-CoV-2 3C-like protease inhibitor approved for use in Japan, demonstrated efficacy as postexposure prophylaxis.¹⁸

In addition to the agents currently recommended for clinical use, a wide array of therapeutic drugs has been evaluated for the treatment of acute COVID-19. Hydroxychloroquine and chloroquine showed in vitro inhibition of viral entry and endocytosis, although not at clinically achievable levels. These findings were not replicated in human studies, with some showing harmful adverse effects like corrected QT interval prolongation.¹⁹ Lopinavir/ritonavir had preliminary clinical evidence against other coronaviruses, but randomized clinical trials have not shown benefit for COVID-19.²⁰ Ivermectin was found to exhibit in vitro inhibition of viral replication only at supraphysiologic concentrations, and randomized clinical trials subsequently demonstrated no clinical benefit in humans.²¹ Therapeutic agents targeting other aspects of the immune response have been tested, but have not demonstrated clear benefit in treating acute COVID-19.¹⁶

Current mainstays of the prevention and treatment of acute COVID-19 include vaccination, antiviral drugs, and anti-inflammatory medications (**Figure 1**). Vaccination, particularly with mRNA-based vaccines, remains the most effective strategy for preventing severe disease. Antiviral

drugs are most effective when used within the first week of symptom onset to reduce viral burden, whereas anti-inflammatory medications should be used in later clinical phases to attenuate pathologic inflammation and associated tissue damage. At symptom onset, oral antiviral drugs like nirmatrelvir/ritonavir and molnupiravir have been shown to reduce disease progression for outpatient

Anti-inflammatory medications should be used in later clinical phases to attenuate pathologic inflammation and associated tissue damage

and inpatient settings, whereas intravenous remdesivir is mainly limited to inpatient settings. In patients with moderate to severe disease, remdesivir should be given to reduce disease progression and mortality risk. In those requiring supplemental oxygen, anti-inflammatory medications such as corticosteroids, baricitinib, tocilizumab, abatacept, and infliximab can be used alongside respiratory support to reduce mortality risk.

Long COVID

There has long been recognition that acute infections can sometimes trigger long-term complications, or post-acute infection syndrome (PAIS).²² Prior to the COVID-19 pandemic, PAIS was largely understudied due to limited

appreciation for the burden of disease and diagnostic limitations compounded by heterogeneity in clinical presentations and a lack of defined biomarkers or assays. Recent global estimates demonstrate that more than one-third of individuals previously infected with SARS-CoV-2 develop long COVID.²³ The scale and homogeneity of the COVID-19 pandemic have enabled large cohort studies to better characterize clinical phenotypes, risk factors, and underlying mechanisms.

The symptom burden and severity of long COVID are variable, although many individuals experience decreased physical and mental health associated with decreased

The workforce reduction from long COVID alongside increased health care utilization has had a substantial impact on the global economy, with a 2024 review estimating an annual economic impact of \$1 trillion

quality of life. In a US-based study comprising more than 100,000 individuals previously infected with SARS-CoV-2, those with long COVID had 28% to 52% higher odds of an unfavorable self-reported general health score.²⁴ Long COVID has a considerable impact on an individual's ability to return to work; approximately 11% to 14% of individuals employed prior to COVID-19 report permanent unemployment in relation to long COVID.²⁵ The workforce reduction from long COVID alongside increased health care utilization has had a substantial impact on the global economy, with a 2024 review estimating an annual economic impact of \$1 trillion, which is about 1% of the global economy.²⁶

The global burden of long COVID is further compounded by a lack of approved therapeutics, which is driven in part by an absence of the following: (1) a defined approach for monitoring disease progression, improvement, or resolution; (2) a clear biologic target for therapeutic intervention; and (3) a reliable definition of long COVID that can accurately inform disease status for inclusion in clinical trials. This is an active area of research, with several national and global networks leading various clinical trials targeting the underlying pathophysiology driving disease and focused on symptom reduction and relief.

The heterogeneity in long COVID manifestations and different working definitions of the syndrome has made

comparisons between cohorts more difficult. More recently, this has improved with the broader adoption of the National Academies of Sciences, Engineering, and Medicine (NASEM) definition of long COVID as a chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects 1 or more organ systems.²⁷ As suggested by this broad definition, long COVID symptoms can involve nearly all organ systems, often including cardiopulmonary complications, neurocognitive dysfunction, gastrointestinal issues, and persistent fatigue, with variable patterns of persistence, resolution, and worsening.²⁸ As summarized in a recent systematic review by Wang and colleagues,²⁹ many groups have attempted to segregate symptom clusters via co-occurrence of symptoms, where reported clusters often include symptoms across numerous organ systems. Fatigue was the most frequently reported symptom across studies and was found to cluster independently or alongside predominately neurocognitive or cardiopulmonary features, supporting the presence of distinct yet overlapping mechanisms underlying specific symptom constellations. Other groups have instead implemented an organ system-based categorization of symptoms, of which neurologic, respiratory, and gastrointestinal symptoms were most common.²⁹ Characterizing co-occurring symptoms may help identify overlapping mechanisms between organ systems and thus guide targeted therapies, whereas the organ system-based approach may help guide a multidisciplinary approach to clinical management in situations where symptoms are too heterogeneous to identify a clear mechanistic pathway.

Various hypotheses informed by acute COVID-19 studies and other types of PAIS have been proposed to

Growing evidence supports several overlapping mechanisms causing long COVID, including persistent viral antigen, immune dysfunction and inflammation, latent viral reactivation, and others

explain the pathogenesis of long COVID.^{22,30,31} Growing evidence supports several overlapping mechanisms, including persistent viral antigen, immune dysfunction and inflammation, latent viral reactivation, mitochondrial dysfunction, gut dysbiosis, and endothelial dysfunction

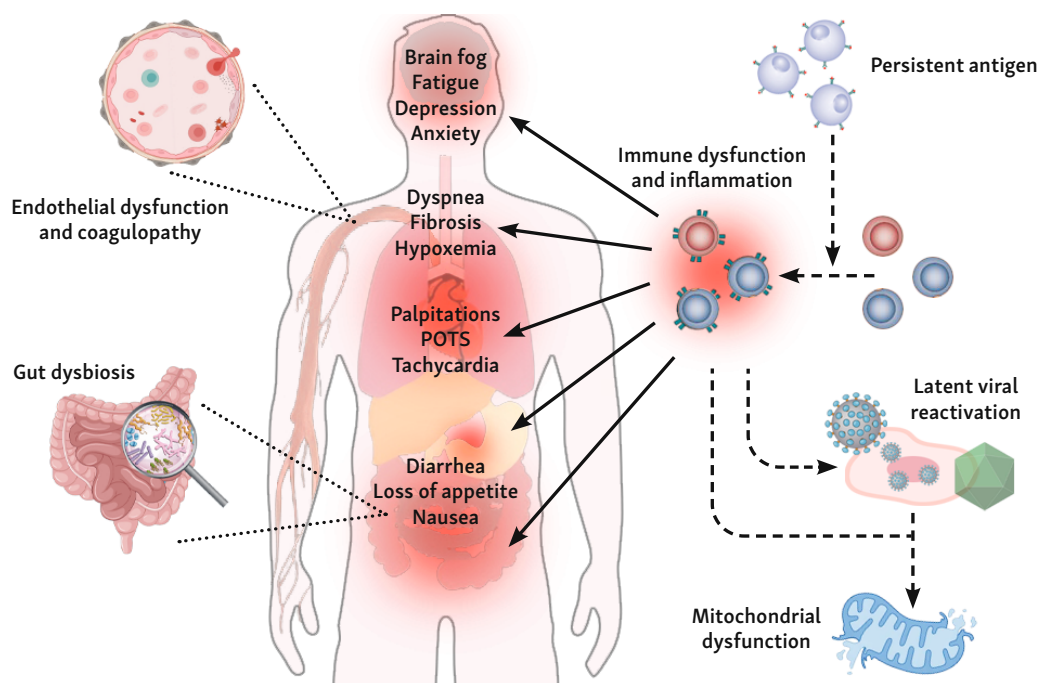


Figure 2. Long COVID symptom mechanisms and examples. Abbreviation: POTS, postural orthostatic tachycardia syndrome.

(**Figure 2**).^{30,31} Potential long COVID therapeutic considerations are outlined in **Figure 3**.

Chronic exposure to viral antigens can drive persistent immune activation and inflammation, increasing the risk of autoimmune and inflammatory conditions.^{30,31} Viruses

such as influenza, Ebola, coxsackie, and SARS-CoV-2 have been associated with PAIS, with some reports finding evidence of antigen persistence.²² SARS-CoV-2 antigens have been detected in various tissues months after infection, raising the possibility of ongoing localized immune activation contributing to organ specific symptoms.³⁰

In a multicohort study, Swank and colleagues detected 1 or more SARS-CoV-2 antigens in 21% of samples collected at least 1 month post infection, with antigen positivity associated with increased odds of having long COVID after adjusting for demographic factors.³² They also found that persistent antigen was more commonly

detected in those experiencing cardiopulmonary, musculoskeletal, and neurologic symptoms, suggesting a shared mechanistic pathway. However, antigen persistence was not detected in all individuals with these symptoms. Persistent antigen has also been detected in asymptomatic

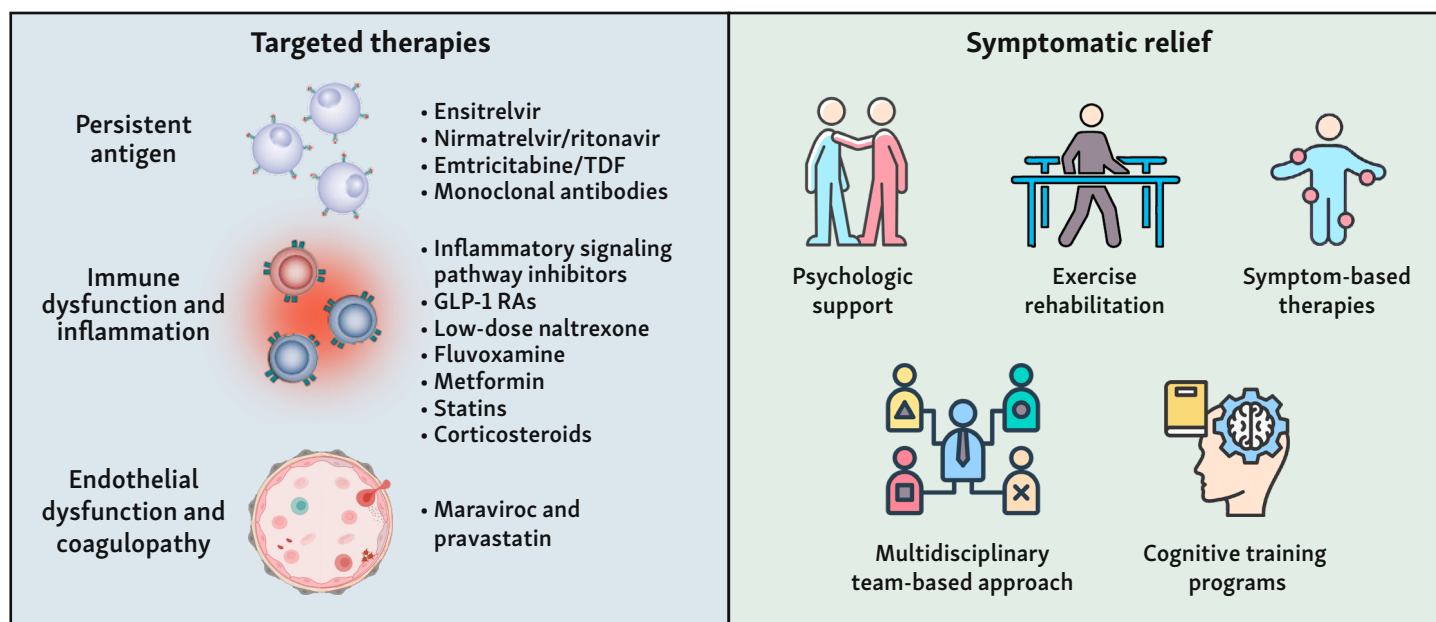


Figure 3. Long COVID therapeutic considerations. Abbreviations: TDF, tenofovir disoproxil fumarate; GLP-1 RAs, glucagon-like peptide-1 receptor agonists.

individuals, further highlighting the need to identify complementary host-response biomarkers and pathways that more precisely distinguish long COVID pathogenesis from residual postacute changes.

Given the potential role of viral persistence, antiviral therapeutics have been identified as a high-priority area of investigation for long COVID. Clinical trials have

Persistent antigen in asymptomatic individuals highlights the need to identify complementary host-response biomarkers and pathways that more precisely distinguish long COVID pathogenesis from residual postacute changes

investigated monoclonal antibodies directed at the SARS-CoV-2 spike protein and antiviral drugs (eg, ensitrelvir, nirmatrelvir/ritonavir, and emtricitabine/tenofovir disoproxil fumarate). Several studies have shown no adverse effects from a 15-day course of nirmatrelvir/ritonavir in individuals with long COVID, but there were no substantial improvements in symptom burden.^{33,34} Most of the trials of other antiviral therapies targeting SARS-CoV-2 are ongoing or have not published data to date. The heterogeneity of enrolled populations may dilute the observed benefits in participant subsets wherein viral persistence is a contributing factor.

Other studies are focused on targeting latent viruses such as cytomegalovirus (CMV) or Epstein-Barr virus (EBV), as infection with another virus like SARS-CoV-2 can lead to reactivation and may contribute to long COVID symptoms in certain individuals. Elevations in EBV- and CMV-specific immunoglobulin G responses have been observed following SARS-CoV-2 infection, supporting the concept that reactivation can occur after acute COVID-19.³⁵ Viral reactivation (eg, of EBV, CMV, or human herpesvirus 6) has been proposed as a driver of myalgic encephalomyelitis/chronic fatigue syndrome (ME-CFS), with some evidence of symptom improvement in patients receiving antiviral therapy targeting herpesviruses.³⁶ These findings suggest that antiviral therapy may be beneficial for selected long COVID endotypes, particularly when combined with therapies addressing downstream inflammation.

Chronic inflammation is involved in many of the mechanisms driving PAIS and is seen in comorbid conditions

such as cardiovascular disease, diabetes, and autoimmune disorders. Although inflammation is normally beneficial, persistent inflammation damages healthy cells and tissues, which could contribute to systemic and organ-specific long COVID symptoms. Several studies have observed an association between certain inflammatory markers (eg, IL-1 β , IL-6, and TNF) and the presence of long COVID.³¹ Inflammatory monocytes and macrophages have been implicated in the pathogenesis of long COVID as producers of inflammatory cytokines and as a potential source of antigen persistence and presentation.³⁷ Other myeloid populations have been implicated in long COVID pathogenesis, although these data are less robust. Similarly, the role of the adaptive immune response is poorly defined. Our group and others have demonstrated persistent SARS-CoV-2-specific B-cell and T-cell responses post infection, particularly among individuals with long COVID, although a clear immune signature has not been identified.^{30,38}

Immune modulators targeting the previously mentioned cytokines and inflammatory pathways (eg, inhibitors of JAK, IL-6, extracellular signal-regulated kinases, and nuclear factor kappa-light-chain-enhancer of activated B-cells) are currently under evaluation. Although there are no published findings in the setting of long COVID, many of these therapies have demonstrated benefit in reducing inflammation and related disease severity in acute COVID-19, as mentioned previously. Other immune modulators such as glucagon-like peptide-1 receptor agonists, low-dose naltrexone, metformin, statins, and corticosteroids are also being studied for their potential in treating long COVID inflammation. Among these, low-dose naltrexone and fluvoxamine have been shown to improve specific symptoms including fatigue, postexertional malaise, and sleep disturbances.^{39,40} Although not a major emphasis, there is a small number of clinical trials on the use of intravenous immunoglobulin for the treatment of long COVID.

There is growing interest in studying tissue-based inflammation and immune responses in the setting of long COVID due to observing persistent antigen, increased metabolic activity, and increased T-cell activation and inflammation in various tissues.³⁰ End organ damage incurred during acute infection can persist and contribute to chronic symptoms. For example, post-COVID-19 pulmonary fibrosis can result from direct virus-mediated damage to alveolar epithelial cells and airway injury during mechanical ventilation.⁴¹ These fibrotic changes can contribute to chronic symptoms such as dyspnea and fatigue.⁴¹ SARS-CoV-2 infection has also been implicated in driving gut mucosal barrier disruption and dysbiosis,

with some studies observing more extensive microbiome changes and higher elevations in indirect markers of microbial translocation (ie, zonulin and β -glucan) in individuals with long COVID than in those who recovered.⁴²

There is growing evidence in support of endothelial dysfunction and clotting as mechanisms behind long COVID, with some studies observing microclots in individuals with long COVID, and persistent elevations in markers of vascular injury and thromboinflammation.^{31,43} Monocytes, which play a role in vascular homeostasis, have been proposed as a potential therapeutic target, with a case series of 18 patients demonstrating long COVID symptom reduction in those treated with maraviroc, a CCR5 antagonist, and pravastatin, a fractalkine inhibitor.⁴⁴

Some of the mechanisms underlying long COVID may not be entirely reversible or easily targeted, and effort has therefore been directed to symptom management. Cognitive training programs (BrainHQ, PASC-Cognitive Recovery [PASC-CoRE], and transcranial direct current stimulation) have been evaluated for their potential use in individuals with long COVID symptoms that impact cognition.⁴⁵ Exercise and rehabilitation-based training programs are also being evaluated in the setting of long COVID, particularly for postexertional malaise and cardiopulmonary symptoms causing exercise intolerance. The implementation of exercise as an intervention targeting long COVID has incorporated lessons from prior research on ME/CFS, in which limited understanding of the underlying mechanisms of the symptoms contributed to potentially harmful recommendations. One trial compared the benefit of in-person exercise programs with virtual exercise training programs in individuals experiencing long COVID approximately 2 years after hospitalization for acute COVID-19, demonstrating improvement in exercise capacity with each training option over standard care alone.⁴⁶ Other trials exploring exercise- and rehabilitation-based therapies are still actively recruiting and ongoing, with no published results to date. Therapies targeting autonomic dysfunction, including stellate ganglion block, ivabradine, and intravenous immunoglobulin, are under active investigation suggesting potential benefit.⁴⁷

Preventative strategies for long COVID are also being studied. Known risk factors for long COVID include female sex, older age, acute COVID-19 severity, vaccination status, obesity, and various comorbidities. Brannock and colleagues observed decreased odds of long COVID in individuals who were vaccinated prior to their acute infection after adjusting for demographic characteristics and medical history.⁴⁸ Antiviral drugs that have proven to be effective during acute COVID-19, including ensitrelvir and nirmatrelvir/ritonavir, are under evaluation for their

potential use in reducing the later development of long COVID. In a phase III clinical trial, ensitrelvir was shown to reduce the risk of developing long COVID, particularly among those with a high number of acute COVID-19 symptoms or a body mass index of 25 kg/m² or higher.⁴⁹ In a retrospective analysis, nirmatrelvir/ritonavir treatment did not have a substantial effect on overall long COVID

Recognizing the potential irreversibility of certain forms of tissue injury, long-term management strategies must also prioritize patient-centered symptom relief and functional recovery

incidence but did have a small protective effect against fatigue and neurocognitive symptoms.⁵⁰ In the same study, researchers found a small protective effect against the overall incidence of long COVID among participants aged 65 years or older. In contrast, studies of tocilizumab or steroids during acute hospitalization showed no difference in long COVID outcomes or health-related quality of life, respectively, up to 1 year post discharge.^{51,52}

Conclusion

Prevention and treatment strategies for acute COVID-19 include vaccination, antiviral therapy, and anti-inflammatory medications. Vaccination remains the most effective approach to prevent severe disease. Antivirals, including nirmatrelvir/ritonavir, molnupiravir, and remdesivir, are most beneficial when initiated early to reduce disease progression, whereas anti-inflammatory therapies are used later in illness to mitigate immune-mediated tissue damage. For patients requiring supplemental oxygen, corticosteroids and selected immunomodulatory agents can reduce mortality rate when used with appropriate respiratory support.

Long COVID is a complex, heterogeneous condition driven by overlapping mechanisms that vary between individuals. Although substantial progress has been made in characterizing potential biologic pathways, targeted therapies remain limited. Future progress will depend on improved patient stratification, validated biomarkers, and mechanism-based trial designs. Given the potential

irreversibility of certain forms of tissue injury, long-term management strategies must prioritize patient-centered symptom relief and functional recovery. 

Financial relationships with ineligible companies within the past 24 months:

Ms Opsteen reported no relevant financial relationships with ineligible companies. (Updated October 20, 2026)
Dr Erdmann reported serving on the data and safety monitoring board for Pfizer, and receiving a patent for his intellectual property (IP), human neutralizing antibodies against SARS-CoV-2/COVID-19, licensed to the Plantform Corporation. (Updated October 23, 2026)

Planner/Reviewer 1 reported no relevant financial relationships with ineligible companies. (Updated October 9, 2026)
Reviewer 2 reported no relevant financial relationships with ineligible companies. (Updated October 12, 2026)
Planner/Reviewer 3 reported no relevant financial relationships with ineligible companies. (Updated October 20, 2026)

All relevant financial relationships with ineligible companies have been mitigated.

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Invited Review

2026 Update on Routine and Special Vaccinations in People With HIV

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Abstract: Vaccinations are an important part of primary care for people with HIV (PWH). They protect against some sexually transmitted infections, and respiratory bacterial and viral infections. PWH are recommended to obtain influenza, COVID-19, herpes zoster (shingles), hepatitis B, meningococcal disease, mpox, and human papillomavirus vaccinations. Additionally, the Advisory Committee on Immunization Practices has released recommendations incorporating the newer formulations of pneumococcal pneumonia vaccines and respiratory syncytial virus vaccines. Considerations for the timing of vaccinations are described, including whether to delay vaccination until improvement of the immune status. Live vaccines (other than nonreplicating vaccines) are contraindicated for PWH with a CD4+ count below 200 cells/ μ L or uncontrolled HIV.

Keywords: COVID-19, hepatitis B, herpes zoster, HIV, HPV, human papillomavirus, immunosuppression, influenza, meningococcus, mpox, pneumococcus, pneumonia, respiratory syncytial virus, RSV, vaccination, vaccine

Introduction

Vaccinations have saved millions of lives by preventing infection or serious manifestations of infection with a variety of illnesses. An estimated 35 infectious diseases have a vaccine that offers some protection.¹ The US Centers for Disease Control and Prevention (CDC) offer guidance for a variety of vaccinations for people with HIV (PWH) including those that protect against sexually transmitted infections (STIs), respiratory illnesses, and serious viral and bacterial infections.² STIs that can be prevented by vaccines include hepatitis B, hepatitis A, human papillomavirus (HPV)-related diseases, and mpox. Additionally, meningococcal disease can be transmitted by close contact including

kissing, coughing, or sharing drinks or utensils. Vaccine protection should be addressed during routine sexual health discussions between practitioners and patients.

Respiratory illnesses can be prevented with vaccination and often occur seasonally, such as the fall/winter pattern seen with influenza and respiratory syncytial virus (RSV) and the bimodal pattern of fall/winter and summer seen with COVID-19. Other bacterial respiratory infections such as pneumococcal infections can accompany viral infections and vaccinations should be addressed as part of routine primary care for PWH.

One consideration when vaccinating PWH is whether to administer the vaccines to individuals who have lower CD4+ cell counts or HIV viremia. **Table 1** summarizes the immunization schedule for PWH as of April 2026 and **Table 2** gives the 2025-2026 COVID-19 vaccine schedule for immunocompromised individuals. **Table 3** provides guidance regarding which vaccines can be given immediately on HIV diagnosis and which can be given after individuals are taking antiretroviral therapy (ART) and

Vaccinations have saved millions of lives by preventing infection or serious manifestations of infection with a variety of illnesses

have virologic suppression and improvement in CD4+ cell count. **Table 4** summarizes recommended vaccines for those who travel outside the US.

Hepatitis A

Hepatitis A is transmitted through the fecal-oral route. PWH are at high risk for severe disease from hepatitis A virus (HAV) infection. Transmission from person to person has been occurring since 2016 in the US. Vaccination is recommended for all PWH aged 1 year and older.⁷ Vaccination for hepatitis A is recommended at 0 months and at 6 to 12 months or in combination with hepatitis B vaccination

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Table 1. Recommended Immunization Schedule for People With HIV, by Age, April 2026^a

Disease(s)	Vaccine recommendation by age			
	9-26 y	27-49 y	50-64 y	≥65 y
Influenza	1 dose annually			1 dose (high dose, recombinant or adjuvanted)
Tdap	1 dose of Tdap, then Td or Tdap booster every 10 y			
Varicella infection	2 doses, 4-8 wk apart (if CD4+ count is ≥200 cells/μL and no immunity to varicella virus)			
HPV	3 doses at 0, 2, and 6 mo	27-45 y ^b		
Herpes zoster infection	Recombinant vaccine, 2 doses at 0 and 2-6 mo			
MMR	2 doses (if CD4+ count is ≥200 cells/μL and no immunity to MMR viruses) at least 1 mo apart			
Pneumococcal disease	PCV20 or PCV21 alone or PCV15 followed by PPSV23 after 8 wk			See ACIP guidance
Hepatitis A	2 or 3 doses depending on the vaccine (if no immunity to HAV) at 0 and 6-18 mo; check HAVAb 1 mo later			
Hepatitis B	2 or 3 doses depending on the vaccine (if no immunity to HBV); Heplisav-B preferred; check HBsAb 1 mo later			
Meningococcal disease	If no prior vaccine, 2 doses of MenACWY 8-12 wk apart, boost every 5 y; group B vaccine given in special circumstances (see ACIP guidance)			
Mpox	2 doses, 28 d apart, for those at risk ^c			
RSV	Seasonal administration between weeks 32 and 36 of pregnancy, September-January		1 dose ^d	1 dose
COVID-19	2025-2026 formulation: 1 dose; immunocompromised individuals can get additional doses ^e			2 doses, 6 mo apart

^aImmunizations should be given after assessment of age, presence of immunity to the pathogen (for hepatitis A and B), and CD4+ cell count. Live replicating vaccines, including those for MMR, varicella infection, and yellow fever, should not be given if CD4+ count is below 200 cells/μL. The oral typhoid and live influenza vaccines are contraindicated in all PWH.

^bHPV vaccination for individuals aged 27 to 45 years should be approached with shared decision-making between the clinician and patient to assess for ongoing risk of exposure to HPV.

^cIndividuals at risk for mpox include those who may have contact with mpox virus through workplace or sexual exposure.

^dRSV vaccination is recommended for persons with cardiopulmonary disease, kidney disorders, liver disorders, neurologic or neuromuscular conditions, hematologic disorders, diabetes mellitus, and moderate or severe immune compromise (attributable to a medical condition or receipt of immunosuppressive medications or treatment); persons who are frail; persons of advanced age; persons who reside in nursing homes or other long-term care facilities; and persons with other underlying conditions or factors that the clinician determines might increase the risk for severe respiratory disease.

^eDose can be given up to 3 mo after infection with COVID-19. See Table 2 for vaccine types and dosing for those who are immunocompromised.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; HAVAb, hepatitis A virus antibody; HBsAb, hepatitis B surface antibody; HPV, human papillomavirus; MenACWY, meningococcal disease caused by serogroups A, C, W, and Y; MMR, measles, mumps, and rubella; PCVx, pneumococcal conjugate vaccine (protects against x serotypes); PPSVx, pneumococcal polysaccharide vaccine (protects against X serotypes); RSV, respiratory syncytial virus; Td, tetanus and diphtheria; Tdap, tetanus, diphtheria, and acellular pertussis.

Adapted from Dunlevy and Johnson.⁵³

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of immunity.

Recommended vaccination for adults with an additional risk factor or another indication.

Recommended vaccination based on shared clinical decision-making.

Table 2. 2025 to 2026 Recommended Initial COVID-19 Vaccine Schedule in Immunocompromised Individuals

Vaccine brand name, manufacturer, type				
	Spikevax, Moderna, mRNA	mNexspike, Moderna, mRNA	Comirnaty, Pfizer-BioNTech, mRNA	Nuvaxovid, Novavax, protein subunit
Dose 1	Day 0	Day 0	Day 0	Day 0
Dose 2	4 wk after dose 1	4 wk after dose 1	3 wk after dose 1	3 wk after dose 1
Dose 3	4 wk after dose 2	4 wk after dose 2	4 wk after dose 2	6 mo after dose 2 (minimum 2 mo) ^a
Dose 4	6 mo after dose 3 (minimum 2 mo) ^a	6 mo after dose 3 (minimum 3 mo) ^a	6 mo after dose 3 (minimum 2 mo) ^a	

^aAny of the 4 vaccines can be substituted for this dose.

Adapted from Dunlevy and Johnson.⁵³

(Twinrix; GlaxoSmithKline) at 0, 1, and 6 months. Immunity is checked prior to vaccination by hepatitis A immunoglobulin G (IgG) antibody testing that demonstrates prior vaccination or infection with development of immunity. Antibody response is assessed at 1 to 2 months after vaccination. If there is incomplete response in the setting of low CD4+ cell count, repeat vaccination should be offered in the setting of recovery of the CD4+ count to more than 200 cells/ μ L.²

Hepatitis B

Hepatitis B virus (HBV) is a common coinfection for PWH who are at increased risk for developing chronic HBV infection.⁸ The incidence of HBV infection has been declining over time, partially due to the availability of hepatitis B vaccination. Tenofovir-containing regimens have activity against HBV, although many individuals who are changing to 2-drug regimens (such as injectable cabotegravir/rilpivirine) do not have hepatitis B surface antibody (HBsAb) for hepatitis B. Given these changes, it will be even more important to vaccinate PWH for hepatitis B. The preferred vaccine in PWH is the recombinant hepatitis B with adjuvant CpG (HBcPcG [Heplisav-B; Dynavax Technologies]) at 0 and 4 weeks. Alternative vaccines are recombinant hepatitis B vaccines (Engerix-B 40 μ g [GlaxoSmithKline] or Recombivax HB 20 μ g [Merck]) or combined hepatitis A and hepatitis B vaccine (Twinrix) at 0, 1, and 6 months. Vaccinated individuals should have HBsAb assessed at 4 weeks after vaccination, with a goal level of 10 mIU/mL or higher. If there is inadequate response to prior Engerix-B or Recombivax HB vaccine, the US Department of Health and Human Services (DHHS) Opportunistic Infections Guidelines recommend Heplisav-B at 0 and 4 weeks with consideration of a third dose at 24 weeks. If there is inadequate response to the initial Heplisav-B vaccination, a

third dose of Heplisav-B at 24 weeks should be administered after the initial dose. The guidelines recommend that hepatitis B vaccination not be deferred based on CD4+ cell

Negative HBsAg and HBsAb and positive HBcAb can indicate a prior infection; these individuals should receive 1 standard dose of hepatitis B vaccine, and HBsAb titers should be assessed 1 to 2 months later

count, but if there is a lack of response to initial vaccination in the setting of a CD4+ cell count below 200 cells/ μ L, repeat vaccination can be delayed until immune recovery.^{2,7}

Negative hepatitis B surface antigen (HBsAg) and HBsAb with positive hepatitis B core antibody (HBcAb) can indicate a prior infection. It is not recommended to routinely check HBV DNA level in this setting but it is recommended to vaccinate these individuals with 1 standard dose of hepatitis B vaccine and check HBsAb titers 1 to 2 months after vaccination. If the HBsAb titer is more than 100 mIU/mL, no further vaccination is needed. If the titer is below 100 mIU/mL, a complete series of hepatitis B vaccinations should follow with HBsAb testing for confirmation of immune response.²

Human Papillomavirus

HPV is a very common cause of disease in the US, with approximately 80% of people having HPV infection at some time. HPV causes more than 39,000 cancers every year in

Table 3. Timing of Vaccination in PWH

Vaccine	CD4+ cell count criteria	Source of advice
Mpox	Give regardless of CD4+ cell count	ACIP guidelines
PCV20, PCV21	Give regardless of CD4+ cell count	NIH HIVMA IDSA OI guidelines ² HIVMA IDSA primary care guidelines ³
PPSV23	Preferably defer until CD4+ count is ≥ 200 cells/ μ L	NIH HIVMA IDSA OI guidelines ²
RSV	Presumably give regardless of CD4+ cell count because it is not a live vaccine	
Tdap	Give regardless of CD4+ cell count	Adult immunization schedule
Typhoid	Inactivated vaccine can be given regardless of CD4+ cell count; oral typhoid vaccine is contraindicated if CD4+ count is < 200 cells/ μ L (OI guidelines) or in all PWH (Yellow Book)	NIH HIVMA IDSA OI guidelines ² CDC Yellow Book ⁴
Varicella	Give only when CD4+ count is ≥ 200 cells/ μ L	Adult immunization schedule
Yellow fever	Give only when CD4+ count is ≥ 200 cells/ μ L	Adult immunization schedule
Zoster recombinant	Give regardless of CD4+ cell count; suggests lower humoral and cellular immune responses in persons with low CD4+ cell counts	Berkowitz et al ⁵
COVID-19	Give regardless of CD4+ cell count	CDC and NIH COVID-19 treatment guidelines
Hepatitis A	Give regardless of CD4+ cell count	NIH HIVMA IDSA OI guidelines ² CDC immunization schedule
Hepatitis B	Give regardless of CD4+ T-cell count; in nonresponders, can delay re-vaccination until CD4+ count is > 200 cells/ μ L and sustained with ART	NIH HIVMA IDSA OI guidelines ²
HPV	Immune responses appear stronger among those with higher CD4+ cell counts and suppressed HIV viral loads	NIH HIVMA IDSA OI guidelines ²
Influenza	Give regardless of CD4+ cell count	Adult immunization schedule
MMR	Give only when CD4+ count is ≥ 200 cells/ μ L	Adult immunization schedule
Meningococcal conjugate	Better immunogenicity if CD4+ cell proportion is $> 15\%$ but deferral is not specifically recommended	Macneil et al ⁶

Abbreviations: ACIP, Advisory Committee on Immunization Practices; ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HIVMA, HIV Medicine Association; HPV, human papillomavirus; IDSA, Infectious Diseases Society of America; MMR, measles, mumps, and rubella; NIH, National Institutes of Health; OI, opportunistic infections; PCVx, pneumococcal conjugate vaccine (protects against x serotypes); PPSVx, pneumococcal polysaccharide vaccine (protects against x serotypes); RSV, respiratory syncytial virus; Tdap, tetanus, diphtheria, and pertussis.

Adapted from Dunlevy and Johnson.⁵³

the US, including cancers of the cervix, vagina, vulva, anus, oropharynx, and penis. Oropharyngeal cancer is the most common cancer in men and cervical cancer is the most common cancer in women.⁹ Rates of anal cancer in some PWH are more than 50-times the rates seen in the general population, with greater risk observed across all PWH.¹⁰ Cervical cancer is the fourth most common cancer worldwide and is more common in PWH. Up to 5% of cervical cancers are attributed to HIV infection.¹¹ HPV vaccination prior to exposure to the virus can prevent more than 90% of HPV-related cancers.

HPV vaccination is recommended for individuals, including PWH, in 3 doses at 0, 1, and 6 months at age 11 or 12 years, starting as early as 9 years. The vaccine is most effective in preventing HPV infections when given at a young age prior to exposure. PWH should not receive the 2-dose vaccine series. The HPV vaccine available in the US is the 9-valent vaccine based on noninfectious viral capsids that protects against HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. Initially, HPV vaccination was only offered up to age 26 years, but the Advisory Committee on Immunization Practices (ACIP) expanded this recommendation in

Table 4. Travel Vaccines

Travel vaccines	If traveling to	Comments
Meningitis	Parts of Africa	
Polio	Nigeria, Afghanistan, Pakistan	Rarely given
Rabies	Many destinations	Prolonged trip, animal exposure
Typhoid	Central and South America, Mexico, Africa, and Asia	
Yellow fever	Parts of Africa and South America	
Cholera	Various destinations	Site of an outbreak, any risk of exposure
Hepatitis A	Central and South America, Mexico, Africa, and Asia	
Hepatitis B	Many destinations	Important if planned sexual activity
Influenza	All destinations	Seasonal by location
Japanese Encephalitis	Parts of Asia	

Adapted from Dunlevy and Johnson.⁵³

2019 for individuals at risk up to age 45 years, with shared clinical decision-making between the patient and their practitioner.¹² Vaccination between ages 27 to 45 years

Although HPV vaccination was initially only offered up to age 26 years, the 2019 ACIP guidelines expanded this recommendation up to age 45 years for individuals at risk, with shared clinical decision-making between the patient and practitioner

is recommended for people with ongoing risk, including those with new sexual partners, and has been shown to be effective and safe in this population. The CDC 5-site Human Papillomavirus Vaccine Impact Monitoring Project demonstrated a decrease in high-grade intraepithelial cervical lesions by 80% in women aged 20 to 24 years from 2008 to 2022 after implementation of vaccination.¹³ Additionally, a Swedish study showed that girls vaccinated prior to age 17 years had an 88% reduction in cervical cancer risk.¹⁴ There is currently no evidence that HPV vaccination reduces the risk of recurrence

of HPV-related high-grade neoplasia in PWH with a history of high-grade neoplasia; however, there are ongoing studies for therapeutic vaccines to treat HPV disease.^{15,16}

Influenza

Although the influenza vaccine is recommended for everyone, some populations have increased risk for medical complications from influenza, including people aged 50 years or older; those with chronic pulmonary diseases, cardiovascular disease, or metabolic disorders (including diabetes mellitus and obesity); those who are immunocompromised; residents of long-term care facilities; and

those who are pregnant. The inactivated influenza vaccine or recombinant influenza vaccine is recommended annually by the ACIP, but the live attenuated influenza vaccines are contraindicated in PWH.¹⁷ For individuals aged 65 years or older, the high-dose, adjuvanted, or recombinant influenza vaccines should be offered.¹⁸ The high-dose vaccine has 4-times the antigen of standard influenza vaccines (60 µg hemagglutinin/strain vs 15 µg hemagglutinin/strain, respectively) and numerous studies have demonstrated a more robust antibody response to the high-dose vaccine conferring increased protection, including in PWH.^{19,20} The recombinant vaccine contains 3-times the hemagglutinin protein (45 µg) as the standard-dose vaccine and has been shown to decrease influenza infections in individuals aged 50 to 64 years.²¹

Measles, Mumps, and Rubella

In the US, measles was declared eliminated in 2000, but the number of infections has been on the rise recently, in part due to decreased vaccination, with fewer than 93% of kindergarteners vaccinated in 2023 to 2024.²² In 2025, there were 2288 confirmed cases, with 243 hospitalizations and 3 deaths. The numbers are increasing in 2026, with 2030 cases already confirmed by June of 2026 in 40 jurisdictions; 92% of infections were in individuals who were unvaccinated or who had unknown vaccination status.²³ The measles, mumps, and rubella (MMR) vaccine is a live, attenuated combination vaccine and is

recommended for nonimmune PWH with CD4+ count of 200 cells/ μ L or higher (contraindicated for those with CD4+ count <200 cells/ μ L) and on ART, with 2 vaccine doses at least 28 days apart. Individuals are considered immune

Measles was declared eliminated in 2000 in the US, but the number of infections has been on the rise recently, with 2287 confirmed cases including 243 hospitalizations and 3 deaths in 2025; 92% of infections were in individuals who were unvaccinated or of unknown vaccination status

if they were born prior to 1957, have documentation of MMR vaccination, or have laboratory evidence of immunity (rubella IgG) or infection. Repeat 2-dose vaccination can be considered in individuals without serologic evidence of immunity. Individuals who are pregnant or are planning to become pregnant should delay vaccination until after pregnancy.² Individuals who received a vaccine from 1963 to 1967 may have received the inactivated measles vaccine, which is less effective and would warrant repeat 2-dose vaccination. Individuals vaccinated prior to 1989 likely only received 1 dose of the MMR vaccine, which is 93% effective. A booster dose of the MMR vaccine should also be given to those who are at a higher risk of exposure, such as health care workers, international travelers, individuals in an area with a measles outbreak, college students, PWH (CD4+ count >200 cells/ μ L), and those around medically high-risk individuals such as those who are immunocompromised.²⁴

Mpox

A worldwide mpox epidemic peaked in the summer of 2022, with ongoing cases seen in 2026, although not nearly at the levels of 2022. In a CDC analysis of 103 individuals hospitalized with mpox, 90 (87%) were PWH and 88% had a CD4+ count below 200 cells/ μ L.²⁵ Twenty of 22 persons who died were PWH and none were on ART. PWH, especially those without viral suppression and with low CD4+ cell counts are at risk for severe disease from mpox. Vaccination against mpox with the nonreplicating modified vaccinia Ankara vaccine (Jynneos; Bavarian Nordic

A/S) with 2 doses 4 weeks apart is recommended for PWH with no prior mpox virus infection who have the potential for mpox exposure (eg, those who are gay or bisexual, men who have sex with men [MSM], transgender or nonbinary individuals with a new STI or sex partner in the past 6 months or partners who meet this description, those who engage in sex at a venue/geographic area where there is ongoing transmission) and PWH who request vaccination. If the second dose is delayed, it can be given as soon as possible without repeating the series. Booster doses are not indicated at this time.^{2,26} Mpox vaccine can also be used as postexposure prophylaxis within 14 days after exposure for those with known exposure, including sex with someone with mpox. Immunogenicity to the nonreplicating mpox vaccine is lower in PWH who are not virologically suppressed or who have CD4+ count below 100 cells/ μ L. Live replicating vaccinia virus vaccines are contraindicated in PWH.

Meningococcal Disease

Although meningococcal disease, which is caused by the *Neisseria meningitidis* bacteria, is not common, there is a 5- to 13-fold higher risk in PWH than in the general population, with increased risk in PWH with a low CD4+ cell count or viremia.⁶ In 2016, 2 meningococcal polysaccharide conjugate vaccines targeting serogroups A, C, W, and Y (MenACWY-CRM [Menveo; GlaxoSmithKline] and MenACWY-TT [MenQuadfi; Sanofi Pasteur]) were recommended for PWH, to be given as a 2-dose series at least 8 weeks apart with a booster every 5 years. The meningococcal ACWY vaccines are interchangeable in adults.

Meningococcal B vaccine is recommended for some PWH, including those aged 16 to 23 years (based on shared decision-making), those at risk (eg, those with

Two recent prospective studies have evaluated meningococcal B vaccine in men who have sex with men, and they did not show a statistical difference in gonorrhea infections for those who received the MenB-4C vaccine

complement deficiency, on a complement inhibitor, or with asplenia), and those affected by outbreaks. Two meningococcal B vaccines are available (MenB-4C [Bexsero;

GlaxoSmithKline] and MenB-FHbp [Trumenba; Wyeth Pharmaceuticals]) and are not interchangeable; PWH should receive the 3-dose series at 0, 1 to 2, and 6 months. There are 2 pentavalent serogroup A, B, C, W, and Y meningococcal vaccines (Penmenvay [using MenB-4C] and Penbray [using MenB-FHbp]); they should be given at 0, 1 to 2 months, and 6 months for PWH needing both meningococcal ACWY and meningococcal B vaccinations.

Given that there are 82 million cases of *N gonorrhoeae* each year worldwide, there has been recent interest in determining whether meningococcal group B vaccine MenB-4C targeting the outer membrane vesicle (OMV) could reduce the incidence of *N gonorrhoeae* infection. OMV is found on *N meningitidis* and on *N gonorrhoeae* bacteria. Retrospective population studies linking vaccination records to cases of gonorrhea in New Zealand and the US showed between 31% and 40% vaccine effectiveness against gonorrhea after administration of the MenB-4C meningococcal B vaccine.^{27,28} A retrospective study of Oregon university students compared the use of 2 meningococcal B vaccines: MenB-4C is OMV based and MenB-FHbp is not.²⁹ The OMV-based vaccine was 47% effective in preventing gonorrhea in this population.²⁹ Two recent prospective studies have evaluated meningococcal B vaccine in MSM. The GoGoVax (Efficacy Study of 4CMenB [Bexsero] to Prevent Gonorrhoea Infection in Gay and Bisexual Men) study was a double-blind, randomized, placebo-controlled study in Australia that demonstrated no difference between vaccinated and unvaccinated individuals in *N gonorrhoeae* infection at pharyngeal, urogenital, or anorectal sites.³⁰ Part of the ANRS 174 DOXYVAC (Combined Prevention of Sexually Transmitted Infections [STIs] in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/Emtricitabine [TDF/FTC] for HIV Pre-exposure Prophylaxis [PrEP]) trial in France included MSM and transgender women (TGW) and compared MenB-4C vaccine with no vaccine. This study showed no statistical difference in *N gonorrhoeae* infections for those who received the MenB-4C vaccine.³¹ Although no significant benefit was seen in MSM and TGW, there is the potential for MenB-4C vaccine to be effective in women, and prospective randomized studies are underway.

Respiratory Syncytial Virus

RSV is more likely to cause hospitalization, lower respiratory tract disease, and death in older adults, with an estimated 60,000 to 160,000 hospitalizations and 6000 to 10,000 deaths annually in the US in those aged 65 years or older. There are 3 types of RSV vaccine licensed for use in the US, including 2 recombinant prefusion F protein vaccines

(RSVPreF3 [Arexvy; GlaxoSmithKline] and RSVpreF [Abrysvo; Pfizer]), and 1 mRNA vaccine (mRESVIA; Moderna). The ACIP recommends that RSV vaccines be given routinely as 1 dose for adults aged 75 years or older and for those aged 50 to 74 years who are at highest risk, based on shared clinical decision-making. Additionally, the ACIP recommends that pregnant women who are at 32 to 36 weeks' gestation during RSV season should be vaccinated with 1 dose of RSVpreF.³² Individuals at the highest risk for severe lower respiratory tract RSV disease include those with chronic lung disease, cardiovascular disease, moderate or severe immunocompromise (including PWH who are not on ART and those with CD4+ count

The ACIP reviewed cases of inflammatory neurologic events after RSV vaccination, and the recombinant prefusion F protein vaccines carry a warning for an increased risk for Guillain-Barré syndrome

<200 cells/ μ L), diabetes, neurologic disorder, neuromuscular disorder, kidney disorder, and liver or hematologic disorders, and individuals who are frail, who are of advanced age, or who are residents of long-term care facilities.³³ In addition, a study evaluated data from RSV-associated hospitalizations to determine characteristics associated with hospitalization and identified obesity as a risk factor.³⁴ Currently, there is insufficient evidence to know if additional doses should be recommended.

The RSVPreF3 and RSVpreF vaccines demonstrated no increased incidence of serious adverse events compared with the placebo arm in initial studies and showed efficacy in preventing symptomatic RSV-associated lower respiratory tract disease over 2 seasons (74.5% and 84.4%, respectively). The ACIP reviewed cases of inflammatory neurologic events occurring within 42 days of RSV vaccination, including Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy, and acute central nervous system inflammation. The US Food and Drug Administration required that RSVPreF3 and RSVpreF vaccines include a warning for GBS because postmarketing observational studies showed an increased risk, with 9 excess cases of GBS per million doses of RSVpreF, and 7 excess cases of GBS per million doses of RSVPreF3 when given to individuals aged 65 years or older.³⁵ Two vaccine studies had

slightly increased episodes of atrial fibrillation, which occurred in 10 participants in each of the vaccine groups and 4 participants in the control arms.^{36,37} This information can be used to inform a discussion on the risks and benefits of this vaccine.

COVID-19

Numerous studies of individuals with COVID-19 have shown worse outcomes in PWH than in the general population. In a large trial examining data from 24 countries from the World Health Organization's Global Clinical Platform, HIV was associated with 15% increased odds of presenting with severe COVID-19 and 38% increased odds of dying in the hospital.³⁸ Increased risk was associated with HIV even with viral suppression. A multicenter cohort study of participants predominantly from the US revealed worse outcomes for PWH including a composite of admission to the intensive care unit, ventilatory support, and death. Additional findings demonstrated worse outcomes for people with a CD4+ count below 200 cells/ μ L, independent of viral suppression.³⁹ PWH were included in

COVID-19 vaccination is recommended for all adults and adolescents with HIV regardless of CD4+ cell count, with a second dose recommended for those aged 65 years or older and for those with advanced or untreated HIV

studies for the 2 types of mRNA vaccine and the glycoprotein vaccine and data support that PWH on ART who have achieved virologic suppression have a good immunologic response to the vaccines. There are currently 4 options for vaccination from 3 different manufacturers, including 3 mRNA vaccines (Comirnaty [Pfizer BioNTech], Spikevax [Moderna], and mRNA-1273 [Moderna]) and 1 glycoprotein vaccine (Nuvaxovid; Novavax).⁴⁰

COVID-19 vaccination is recommended for all adults and adolescents with HIV regardless of CD4+ cell count. A second dose of COVID-19 vaccine is recommended for those aged 65 years or older and for those with advanced or untreated HIV.⁴⁰ The vaccine schedule for initial doses of COVID-19 in immunocompromised individuals (including those with advanced HIV) is seen in **Table 2**. Some studies that show benefit in the general population can be useful for discussion with vaccine-hesitant patients. An

observational cohort from the Veterans Administration compared veterans aged 18 years or older who received influenza and COVID-19 vaccines with those who received influenza vaccine alone in 2024 and 2025. The COVID-19 vaccine effectiveness was noted to be 29% for COVID-19 emergency department visits, 39% for COVID-19 hospitalizations, and 64% for COVID-19 deaths.⁴¹ The CDC reported that during 2024 and 2025, vaccine effectiveness for COVID-19 in those aged 18 years or older was 33% for emergency department/urgent care visits. In those aged 65 years or older, vaccine effectiveness was 45% for hospital admission, decreasing to 40% in those with immunocompromising conditions.⁴²

Pneumococcal Disease

PWH, including those on ART, are at higher risk for invasive *Streptococcus pneumoniae* infections than the general population.^{43,44} Several new pneumococcal vaccines have recently become available, substantially changing the recommendations for vaccination. A study demonstrated the immunogenicity and safety of the 15-valent pneumococcal conjugate vaccine (PCV15) followed by the 23-valent pneumococcal polysaccharide (PPSV23) vaccine in PWH.⁴⁵ Although PCV20 was not specifically studied in PWH, serotypes covered by PCV20 that are not covered by PCV15 make up 16.5% of cases of invasive pulmonary disease, which supports the use of PCV20 if available to reduce the burden of disease. PCV21 contains 8 new pneumococcal serotypes that were not included in PCV15, PCV20, or PPSV23. However, PCV21 does not contain certain pneumococcal serotypes included in other pneumococcal vaccines. PCV21 does not include serotype 4, which causes more than 30% of pneumococcal disease in western US areas with surveillance (Alaska, Colorado, New Mexico, the Navajo Nation, and Oregon). The rates of serotype 4 in areas without surveillance are unknown.⁴⁶ The National Institutes of Health Community-Acquired Pneumonia Section Group of the Adult and Adolescent Opportunistic Infections Guidelines Panel states that PCV21 is not recommended for adult PWH if the prevalence of serotype 4 is above 30% in the region.^{2,47}

The CDC recommends pneumococcal vaccination in adults aged 50 years or older and in those aged 19 to 49 years who are at risk for pneumococcal disease, including PWH. PWH without a history of pneumococcal vaccination or who only received a PCV7 vaccine can be vaccinated with PCV20 (Prevnar 20; Pfizer) or with PCV21 (Capvaxie; Merck) alone or a combination of PCV15 (Vaxneuvance; Merck) with PPSV23 (Pneumovax; Merck) administered 8 weeks later. If there has been a PCV13 vaccination, PCV20 or PCV21 can be given 1 year later. If there has been a

PPSV23 vaccination before age 65 years, a dose of PCV15, PCV20, or PCV21 should be given at least 1 year after the last PPSV23 dose. Finally, if individuals aged 65 years or older have received PPSV23 previously, shared decision-making is recommended to determine whether to offer PCV21 or PCV20 at least 5 years after the last pneumococcal vaccine dose.⁴⁸

Herpes Zoster

Herpes zoster, commonly termed shingles, is caused by reactivation of the varicella zoster virus and is a common complication in PWH, with rates more than twice as high as a cohort of individuals who were HIV negative in the Veterans Aging Cohort Study. Individuals with HIV viral suppression in groups aged younger than 60 years and those aged 60 years or older had higher rates of herpes zoster than comparative age groups of individuals without HIV.⁴⁹ Guidelines recommend vaccination in all PWH aged 18 years or older with 2 doses of the recombinant adjuvanted zoster vaccine (RZV) at 0 months and 2 to 6 months. Individuals who previously received the attenuated live zoster vaccine (discontinued, previously sold as Zostavax; Merck) should be revaccinated with RZV. The NIH HIVMA IDSA opportunistic infections guidelines note that some experts recommend delaying vaccination until viral suppression is achieved on ART or until the CD4+ count is above 200 cells/ μ L. RZV is not recommended during pregnancy.² The varicella vaccine is recommended for individuals without prior vaccination or immunity to varicella. Given that this is a live vaccine, it is contraindicated for individuals with a CD4+ count below 200 cells/ μ L. The vaccine is given as 2 doses, 4 to 8 weeks apart.²

Vaccine Hesitancy

Vaccine hesitancy is a state of indecision and uncertainty that precedes a decision to become (or not become) vaccinated. Through the internet and social media, information shared about vaccines may not be scientifically based. It is not surprising that with this level of disinformation, patients may have questions or express hesitancy about receiving vaccines. As described above, there are many vaccines recommended for PWH and it can be overwhelming for the patient to process the risks and benefits, especially after a new diagnosis of HIV. Studies show that individuals respond well to receiving their vaccine information from a trusted physician.⁵⁰ Motivational interviewing is a particularly effective tool for supporting individuals in making informed decisions about vaccination. Understanding the individual perspective and why they are hesitant and guiding them through motivational

interviewing can increase vaccine uptake. Motivational interviewing incorporates listening to the patient, responding to their concerns, and connecting their values to the benefits of vaccines rather than simply providing facts on vaccination.⁵¹ Vaccination is often not emergent and ongoing discussions with patients over numerous visits may lead to improvement in vaccination rates. Reliable recommendations on vaccination can be found through the NIH HIVMA IDSA opportunistic infections guidelines, professional societies (such as the Infectious Diseases Society of America and the American Academy of Pediatrics) and the University of Minnesota Center for Infectious Disease Research and Policy.^{2,52}

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Financial relationships with ineligible companies within the past 24 months:

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All relevant financial relationships with ineligible companies have been mitigated.

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Invited Review

Drug-Drug Interactions, Dosing, Formulations, and Other Pharmacologic Issues in HIV Management: A Week on Consultation With Your HIV Clinical Pharmacologist

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Abstract: Antiretroviral therapy is highly effective, but variability in HIV drug exposure can lead to differences in treatment efficacy, toxic effects, and the emergence of resistance. Each HIV clinician should have a detailed knowledge of HIV clinical pharmacology, including the management of drug-drug interactions, appropriate dosing, and the influence of different formulations. This review illustrates these concepts using a series of consultations with an HIV clinical pharmacologist during a typical week.

Keywords: antiretroviral drugs, drug-drug interactions, drug resistance, HIV, pediatric HIV, pharmacokinetics, pharmacology, therapeutic drug monitoring

Introduction

More than 30 years ago, with the introduction of the first effective combination antiretroviral (ARV) regimen, it became apparent that the drugs could exhibit substantial variability in treatment response among people with HIV (PWH). The pharmacokinetic profiles of HIV protease inhibitors, which were introduced around 1996 and included zidovudine, zalcitabine, and didanosine, were not optimal and exhibited limited absorption, short elimination half-lives, and high susceptibility to drug-drug interactions (DDIs). Adherence of more than 95% was needed to achieve sustained virologic suppression and to prevent the emergence of drug resistance.

Pharmacology has played a crucial role in HIV prevention and treatment, and clinical pharmacologists have contributed through research, education, and

clinical consultation to optimize outcomes. These contributions have spanned from the early days of protease inhibitor-based triple therapy to more recent innovations such as long-acting injectable cabotegravir/rilpivirine (LA CAB/RPV).

One of the basic principles of clinical pharmacology is the concentration-effect relationship, ie, without drug exposure, there is no pharmacologic activity. In 1538, the Swiss physician Paracelsus stated that “every substance can be toxic, dependent on the dose” or, to put it in terms of current clinical understanding, dependent on the concentration. In modern clinical pharmacology, these principles have been developed into the concept of a therapeutic range (**Figure 1**). Ideally, every patient on the same dose of a medication maintains a plasma concentration within the therapeutic range during the entire dose interval. A certain threshold concentration is needed to inhibit viral enzymes such as HIV protease and integrase, to maintain virologic suppression. However, many factors can influence pharmacokinetic variability, leading to toxic or to subtherapeutic levels of the ARV agent. Knowledge of these factors is crucial for the optimal care of PWH. HIV clinical pharmacologists provide specialized expertise

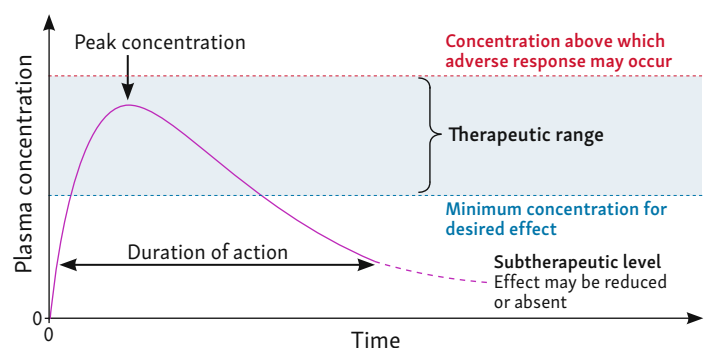


Figure 1. Therapeutic range (or “window”): concentrations associated with desired clinical effect and acceptable tolerability. Adapted from Smith R.²⁴

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and collaborate with health care practitioners to improve outcomes in PWH. To illustrate the role of clinical pharmacology in optimizing HIV care, this review presents a week in the life of a clinical pharmacologist, highlighting real-life consultations in which pharmacologic expertise contributed to the clinical management of PWH.

Monday

Dr M. calls: "We have a patient on dolutegravir [DTG]/lamivudine, with a well-suppressed viral load and a suspected

Rifampicin is a strong inducer of CYP3A and UGT1A1, which are hepatic enzymes that are responsible for dolutegravir metabolism

prosthetic valve endocarditis with a coagulase-negative Staphylococcus aureus. We would like to add rifampicin 600 mg twice daily to treat the biofilm. With rifampicin 600 mg once daily, we need to adjust the dose of DTG to 50 mg twice daily. What is your advice for this higher dose of rifampicin?"

Dr M. is an HIV physician and is aware of the well-known DDI between rifampicin and DTG.¹ Rifampicin is a strong inducer of cytochrome P450 3A (CYP3A) and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which are hepatic enzymes that are responsible for DTG metabolism. Trough levels of DTG will be reduced by 72% or more, leaving the individual at risk of virologic failure. To manage this DDI, the DTG dose should be increased from 50 mg once daily to 50 mg twice daily. This is described in the prescribing information of DTG-containing regimens and is also available in online DDI resources such as the HIV Interaction Checker developed by the University of Liverpool.²

In this individual, however, a higher dose of rifampicin is being prescribed, leading to the question of whether the higher dose will result in a stronger induction of metabolic enzymes, or whether the capacity is already maximal at the standard dose of 600 mg daily. If there is a stronger induction of CYP3A and UGT1A1, is DTG 50 mg twice daily still sufficient? This question is relevant in this patient with *S aureus* infection and in individuals with tuberculosis (TB), in whom higher doses of rifampicin (up to 35 mg/kg) are being tested to shorten the treatment duration.³

This specific research question has been addressed in the SAEFRIF (Pharmacokinetics, Safety/Tolerability, and Efficacy of High-Dose Rifampicin in Tuberculosis-HIV Coinfected Patients on Efavirenz- or Dolutegravir-Based Antiretroviral Therapy: Study Protocol for an Open-Label, Phase II Clinical Trial) study at the TB-HIV outpatient clinic of the Infectious Diseases Institute at Makerere University in Uganda.⁴ PWH who were newly diagnosed with TB were randomly assigned to standard-dose (10 mg/kg) or to high-dose (35 mg/kg) rifampicin as part of their standard TB regimen. Participants were on or planning to start DTG-containing ARV therapy. DTG was dosed at 50 mg twice daily in accordance with the prescribing information and switched to once daily 2 weeks after completing TB treatment because the enzyme-inducing effects of rifampicin slowly reverse over a period of 1 to 2 weeks. Pharmacokinetic sampling for DTG trough concentrations was performed during and after rifampicin coadministration, enabling intraparticipant comparisons. The data showed that DTG trough levels averaged 0.46 mg/L with high-dose rifampicin and 0.80 mg/L with standard-dose rifampicin; the latter value is close to measurements in patients on DTG 50 mg once daily without rifampicin. Thus, as an interim conclusion, high-dose rifampicin does provide a higher level of enzyme induction than standard-dose rifampicin.

The next question is whether this information is clinically relevant, which depends on the therapeutic range of DTG. Two thresholds have been proposed in the literature. The first, 0.3 mg/L, is the average concentration of lower doses of DTG that have been shown to be noninferior to 50 mg once daily⁵ and can therefore be seen as a conservative threshold. The second, 0.064 mg/L, is the protein-adjusted 90% inhibitory concentration value for DTG and can be seen as the absolute minimum concentration required for ARV activity. In this study, there was a lower proportion of individuals on high-dose rifampicin achieving the 0.30 mg/L threshold than in those on standard-dose rifampicin (60.9% vs 92.9%, respectively; $P=.014$); for the 0.064 mg/L threshold, there was no difference in proportion of individuals achieving that goal ($P=.999$). Viral load responses in the rifampicin groups were similar, suggesting that the 0.064 mg/L threshold as a target makes more sense than the conservative value of 0.30 mg/L.

In the individual described above, despite stronger enzyme induction caused by higher-than-standard doses of rifampicin, it is very likely that DTG trough levels with 50 mg twice daily dosing will remain in the therapeutic range. There is therefore no reason to change the standard management of this DDI.

Tuesday

Dr J. approaches you at a meeting: “I recently saw a 27-year-old man with HIV who switched from doravirine/lamivudine/tenofovir disoproxil fumarate [TDF] to injectable LA CAB/RPV every 2 months and developed virologic failure after 8 months of treatment. Resistance testing showed mutations for CAB [N155S] and RPV [E138K]. HIV-1 was retrospectively

High concentrations of testosterone due to supplemental injections can cause enzyme induction, and possibly lower drug levels of CAB and RPV

analyzed and determined to be subtype A6. He is a body builder and is taking anabolic androgen steroids and testosterone and has a muscular physique and a body mass index [BMI] of 35 kg/m². Do you think the anabolic steroids have influenced the hepatic metabolism of the CAB or RPV? Can you do drug levels?”

LA CAB/RPV is a highly effective treatment but confirmed virologic failure may occur in 1% to 2% of cases after 1 year of treatment, often with multiclass drug resistance. Clinical trials have shown that subtype A6, preexisting RPV mutations, and BMI above 30 kg/m² are risk factors for virologic failure, with an increased risk observed only in individuals with at least 2 of these factors.⁶ Low CAB or RPB levels increase this risk of virologic failure but the clinical relevance in the absence of other risk factors remains to be determined.

To assess whether a DDI may be involved in this case, it is first necessary to review what is known about the effect of enzyme inducers on the pharmacokinetics of LA CAB/RPV injections. During clinical drug development, studies were performed with rifampicin and oral CAB and RPV (showing >80% reductions in trough levels of these agents) but data are lacking on the impact of rifampicin (or other enzyme inducers) on LA intramuscular injections of these agents. In this case, physiologically based pharmacokinetic modeling may be helpful, predicting that when used with rifampicin, overall exposure to CAB will be reduced by 61% and overall exposure to RPV will be reduced by 38%.⁷

The next question is whether anabolic steroids can behave as an enzyme inducer (like rifampicin), but this has not been investigated in detail. Data from more than 30 years ago demonstrated that propranolol glucuronidation correlated with testosterone levels;⁸ in other words, high concentrations of testosterone due to supplemental

injections can cause enzyme induction, and possibly lower drug levels of CAB and RPV.

Another, more indirect explanation for the altered pharmacokinetics of CAB/RPV in this individual is his intensive bodybuilding activity, which may have contributed to faster drug release from the intramuscular depot. Finally, a single case of faster elimination of CAB/RPV in a young athletic person injecting anabolic steroids has been reported.⁹

Therapeutic drug monitoring may be useful in this situation, provided it is available. Fortunately, it is routinely available in the Netherlands. We therefore measured the trough concentrations and determined them to be 0.91 mg/L for CAB and 0.026 mg/L for RPV. These values are 43% lower and 61% lower, respectively, than reported median population values, suggesting an enzyme-inducing effect.

As discussed in the previous case, not every reduction in trough level is clinically relevant. The clinical significance depends on the size of the reduction and the width of the therapeutic range. There is much debate regarding therapeutic targets for CAB and RPV,¹⁰ but the consensus in the Netherlands is 0.66 mg/L for CAB and 0.032 mg/L for RPV, which means that the DTG level is still therapeutic, but the RPV level is subtherapeutic. In combination with the presence of the A6 subtype, which only became apparent at confirmed virologic failure, and the high BMI, which was not considered to be obesity by the treating physician, lower levels of RPV in particular may have contributed to the virologic failure in this patient.

Although this potential DDI was recorded after virologic failure had been documented, sharing the insights gained from such cases in peer-reviewed journals remains valuable despite the inherent limitations of case reports.¹¹ An alternative to formal publication is submitting cases with suspected DDIs to the Clinical Cases DDI platform.¹² Case submissions are reviewed by the editorial board and this platform can facilitate the rapid dissemination of clinically relevant information when information is incomplete or there is insufficient time to prepare a manuscript for traditional publication channels.

Wednesday

You attend the weekly HIV outpatient rounds and Mr V. is discussed. He is a 63-year-old man who was diagnosed with HIV in 2011. He is currently virologically suppressed on LA CAB/RPV but, for logistic reasons, needs to switch to a daily oral ARV regimen. The treating physician wants to start the patient on DTG/lamivudine but a DDI alert is generated because he is currently taking metformin 1500 mg daily. His

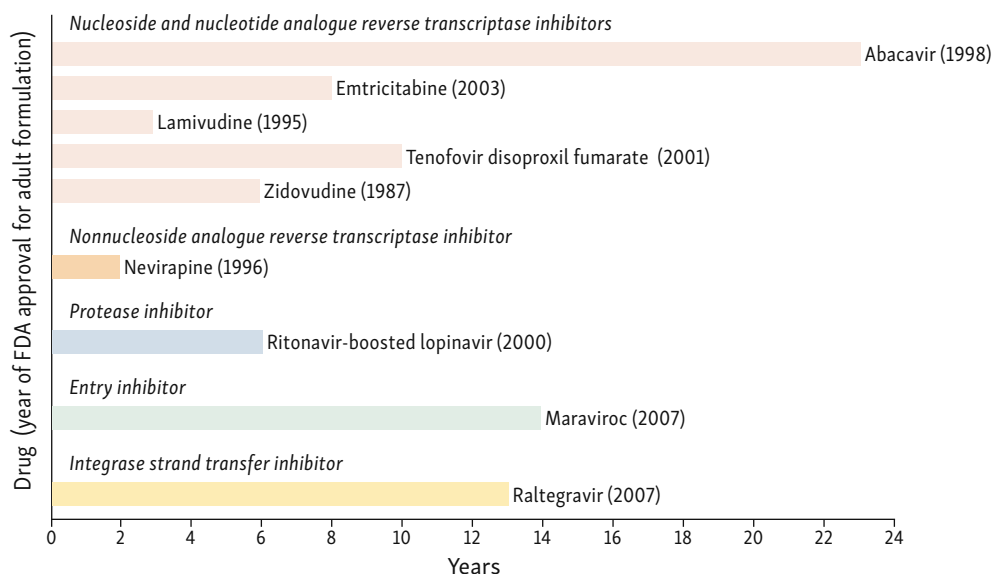


Figure 2. Time between year of US Food and Drug Administration (FDA) approval for adult formulation and first pharmacokinetic data for neonates published in a peer-reviewed journal by 2021. The median time until neonatal pharmacokinetic data are available is 8 years. Adapted from Jacobs TG and colleagues.¹⁷

BMI is 35 kg/m². Should the metformin be replaced with an SGLT2 inhibitor because of the high BMI?

Metformin is one of the most widely used medications worldwide, and its use will increase in the aging population of PWH. However, metformin is associated with DDIs with certain HIV drugs, in particular DTG, because the plasma concentrations of metformin increase through the inhibition of the renal efflux transporter, organic cation transporter 2 (OCT2). A healthy volunteer study showed that the metformin area under the plasma concentration-time curve (AUC) increased by 79% when coadministered with DTG once daily, potentially leading to metformin-associated toxicity.¹³

It is important to note that DDIs can be managed through a variety of strategies. A DDI alert does not always indicate that a combination of drugs is contraindicated. In this particular patient, a number of options are available for consideration:

1. Replace the precipitant drug (DTG → ?)
2. Replace the object drug (metformin → ?)
3. Modify the dose of the object drug (metformin)
4. Intensify patient monitoring (blood glucose, adverse events)

Each of these options may be appropriate, depending on patient-specific considerations. For instance, with option 1, bictegravir may be a good alternative to DTG because it causes less potent inhibition of OCT2, resulting in a less pronounced increase in metformin plasma concentration.¹⁴ Alternatively, with option 2, seeking an alternative

to metformin, the Interaction Checker of the University of Liverpool may prove useful, as one can search by drug class and determine that SGLT2 inhibitors such as canagliflozin, dapagliflozin, and empagliflozin are not associated with a DDI with DTG. Modifying the metformin dose, as with option 3, is a rational intervention because it minimizes the risk for toxicity while maintaining metformin plasma concentrations within the therapeutic range. Over the last 13 years, the US Food and Drug Administration (FDA)-approved prescribing information for DTG has evolved regarding the management of DDI with metformin. Initially, in 2013, the DTG prescribing information stated that a dose adjustment of metformin may be necessary; however, in 2019, it was updated to recommend limiting the dose of metformin to 1000 mg daily. Currently, in 2026, no specific recommendation is provided other than a reference to the metformin prescribing information. In this context, a recent publication

from South Africa is noteworthy.¹⁵ In this study, individuals receiving DTG and metformin underwent the standard metformin dose reduction to 1000 mg daily; however, suboptimal glycemic control occurred among women who were obese. Thus, although a dose reduction might be appropriate in a particular individual, it may not be suitable in all cases.

Although a metformin dose reduction might be appropriate in a particular individual, it may not be suitable in all cases

Finally, is option 4, ie, intensifying the monitoring of blood glucose levels and adverse events, followed by individualized adjustment of the metformin dose. With this approach, the presence of a DDI is only one factor among several considerations. This option was accepted by the HIV physician and the patient, demonstrating that a DDI alert does not always require a change in medication.

Thursday

You receive a call in the very early hours of the morning on your private cell phone from an HIV pediatrician: “We have a neonate prematurely born at a gestational age [GA] of 24 weeks and 4 days to a mother with HIV. The mother’s HIV has been undetectable since 2016. The baby received zidovudine for 4 weeks after birth and has not been breast-feeding. The first HIV test, performed within 24 hours of birth, was negative. However, 6 weeks after birth, 2 weeks after zidovudine treatment was terminated, the HIV RNA level was 1.9×10^5 copies/mL. Today, 3 days later, the HIV RNA level is 1.2×10^7 copies/mL. Current GA is 31 weeks and the neonate weighs approximately 1 kg. Resistance testing results are expected on Monday. We would like to discuss the treatment options for this neonate with you as soon as possible.”

In 2008, Violari and colleagues demonstrated that early treatment of infants with HIV saves lives.¹⁶ Although access to the most potent ARV drugs, such as integrase strand transfer inhibitors, has improved for children with HIV, data for neonates are lacking. In 2022, Jacobs and colleagues published a viewpoint article¹⁷ to stimulate pharmacokinetic studies in neonates with HIV to accelerate access to therapeutic drugs. This review examined the first pharmacokinetic data in newborns for all ARV agents and noted a median lag time of 8 years after FDA approval of the adult formulation (**Figure 2**).

Current guidelines, therefore, still recommend older ARV agents such as zidovudine and nevirapine (plus lamivudine) for term and preterm infants with a postmenstrual age of more than 32 weeks. Raltegravir is an alternative to nevirapine in term infants weighing at least 2 kg. The neonate in the current case was preterm, with a postmenstrual age of 31 weeks. Furthermore, nevirapine is not a recommended choice for patients with a high viral load. More modern agents such as DTG would be more attractive options.

Importantly, in 2025, the PETITE-DTG (Safety and Pharmacokinetics of Dolutegravir Dispersible Tablets and Oral Films in Term Neonates Exposed to HIV in South Africa) study¹⁸ presented the first data on the pharmacokinetics of DTG in neonates. Bekker and colleagues used a 2-stage approach: in stage 1, a single dose of DTG 5 mg was administered to neonates exposed to HIV who weighed at least 2 kg and who were receiving standard postexposure prophylaxis. A pharmacokinetic model was built and safety was evaluated. In stage 2, newborns receiving standard postexposure prophylaxis received chronic dosing of DTG 5 mg every 48 hours in weeks 1 and 2, and DTG 5 mg every 24 hours in weeks 3 and 4. DTG was well tolerated, target concentrations were achieved, and none of the newborns

acquired HIV. The authors concluded that their data supported the inclusion of DTG in national and international guidelines.

Based on the PETITE-DTG study data, the abovementioned neonate was given a smaller dose of DTG (2.5 mg every 48 hours) in combination with zidovudine plus lamivudine because this child was preterm and had a body weight of only 1 kg. DTG plasma concentrations were measured at 2 hours, 24 hours, and 48 hours. Results were 2.1 mg/L, 0.54 mg/L, and 0.42 mg/L, respectively. The elimination half-life was estimated to be 69 hours, which is severely prolonged (adult elimination half-life, 14 h). The concentration at 48 hours was above the conservative target of 0.30 mg/L for DTG. Over time, DTG doses were adjusted based on changes in body weight and supported by therapeutic drug monitoring.

Friday

You are invited to a meeting of the national HIV Preexposure Prophylaxis [PrEP] Guidelines Committee. During the coffee break, a committee member approaches you: “We increasingly see patients who have undergone bariatric surgery and are candidates for oral PrEP with TDF/emtricitabine [FTC]. What should we tell them? Is bariatric

There is no indication that a history of bariatric surgery influences TDF/FTC absorption, and daily PrEP should therefore be effective

surgery a contraindication to TDF/FTC PrEP? Should we adjust the dose of TDF/FTC? Is there a role for pharmacokinetic measurements? Are tenofovir alafenamide/FTC, intramuscular CAB, or subcutaneous lenacapavir appropriate alternatives?”

TDF/FTC is highly effective for HIV PrEP when taken with good adherence, but its efficacy is dependent on good absorption. It is unknown whether bariatric surgery was an exclusion criterion for subjects in the pivotal PrEP trials. Kingma and colleagues described general concepts of oral drug dosing following bariatric surgery. They concluded that in the absence of well-performed studies, it is difficult to provide recommendations in those who have undergone bariatric surgery, and that risk assessment is required on an individualized basis.¹⁹

Data on the pharmacokinetics of TDF/FTC treatment in PWH who have undergone bariatric surgery demonstrate that the plasma trough levels of tenofovir are generally around 0.05 mg/L, which is similar to levels in those who have not undergone bariatric surgery.²⁰ In some case reports, data have been collected before and 3 to 6 months after bariatric surgery, and demonstrate no influence from the surgery.²¹ Data on tenofovir pharmacokinetics in PrEP users are much more limited, but do not suggest a major impact.²² The data reported to date are on individuals taking daily oral PrEP, with the exception of 1 patient who used on-demand PrEP and who appeared to have a low tenofovir concentration.²²

TAF/FTC is FDA approved in the US for HIV PrEP. The intracellular pharmacokinetic measurements of tenofovir diphosphate in a small number of individuals do not suggest a major impact from bariatric surgery.²³ However, in areas where PrEP is not publicly funded or reimbursed, TAF/FTC is substantially more expensive than generic TDF/FTC, which may limit its use.

Finally, LA agents such as intramuscular CAB and subcutaneous lenacapavir have the theoretic advantage of bypassing gastrointestinal absorption and may be attractive alternatives when available and affordable.

In summary, there is no indication that a history of bariatric surgery influences TDF/FTC absorption, and daily PrEP should therefore be effective.

Conclusion

Collectively, this week of consultations demonstrates that clinical pharmacology is an important tool for optimizing the treatment of PWH. Its applications to DDIs, dosing, and adverse effects help to inform HIV prevention and treatment decisions in routine clinical care. The cases also illustrate the ongoing need to integrate pharmacologic principles into the management of HIV ARV regimens. 

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All relevant financial relationships with ineligible companies have been mitigated.

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