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Topics in Antiviral Medicine™

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Invited Reviews

Case Report

Topics in Antiviral Medicine™

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On completion of this activity, which contains 4 articles, the learner will be better able to:

- Summarize current information on mRNA vaccine technology and describe how it was successfully used during the COVID-19 pandemic and has created opportunities in the ongoing search for an effective HIV-1 vaccine.
- Utilize the latest recommendations for routine and special vaccinations in people with HIV.
- Describe the experiences, clinical manifestations, and perspectives of 2 physician-patients suffering from long COVID.
- Outline the long-term treatment regimen for a patient who developed highly drug-resistant HIV with a well-documented evolution of resistance with serial genotyping and phenotyping drug resistance tests.

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Invited Review

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) and can protect against viral hepatitis and some sexually transmitted infections, as well as respiratory bacterial and viral infections. Vaccinations for influenza, COVID-19, herpes zoster (shingles), hepatitis B, meningococcal disease, mpox, and human papillomavirus are recommended for PWH. Additionally, the Advisory Committee on Immunization Practices has released recommendations incorporating the newer formulations of the pneumococcal pneumonia and respiratory syncytial virus vaccines. Additional considerations for the timing of vaccinations are described, including whether to delay vaccination until improvement of the immune status. Live vaccines (other than nonreplicating) are contraindicated for PWH with CD4+ counts less than 200 cells/μL or uncontrolled HIV.*

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

Introduction

Vaccinations have saved millions of lives by preventing infections or serious manifestations of infections. An estimated 34 infectious diseases have a vaccine that offers some protection.[1] The Centers for Disease Control and Prevention (CDC) offers guidance for a variety of vaccinations for people with HIV (PWH), including those that protect against sexually transmitted infections, respiratory illnesses, and other serious viral and bacterial infections.[2]

Viruses that can cause sexually transmitted infections that can be prevented by vaccines include hepatitis B virus (HBV), hepatitis A virus (HAV), human papillomavirus (HPV), and mpox virus. Additionally, meningococcal disease can be transmitted by close contact including kissing, coughing, or sharing drinks or utensils. Vaccine protection should be addressed in routine sexual health discussions between clinicians and patients.

Many respiratory illnesses can be prevented by vaccination and often occur seasonally, such as the fall/winter pattern seen with influenza and respiratory syncytial virus (RSV). Other bacterial respiratory infections, such as pneumococcal infections, can accompany viral infections. Vaccinations should be discussed during routine primary care visits for PWH.

One consideration for vaccinations for PWH is whether to administer the vaccines to individuals who have low CD4+ cell counts or HIV viremia. Table 1 provides guidance around which vaccines can be given immediately regardless of the CD4+ cell count and which can be delayed until after PWH are taking antiretroviral therapy (ART) and have improvement in CD4+ cell count, Table 2 and Table 3 outline recommended immunizations for PWH stratified by age, and Table 4 provides recommendations for travel vaccines in PWH.

Influenza Virus

The influenza vaccine is generally recommended for everyone, but some populations have an increased risk for medical complications from influenza, including people aged 50 years and older; those with chronic pulmonary disease, 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. Annual inactivated influenza vaccine or recombinant influenza vaccine is recommended by the Advisory Committee on

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Table 1. Timing of Vaccination in People With HIV

Vaccine	CD4+ count criteria	Source
Mpox	Give regardless of CD4+ count	ACIP guidelines[3]
PCV20	Give regardless of CD4+ count (OI guidelines) or when CD4+ count is ≥200 cells/μL	OI guidelines[2]
PPSV23	Preferably defer until CD4+ count is >200 cells/μL	OI guidelines[2]
RSV	Presumably give regardless of CD4+ count as it is not a live vaccine and is given in the fall	—
Tdap	Give regardless of CD4+ count	Adult immunization schedule[4]
Varicella	Give only when CD4+ count is ≥200 cells/μL	Adult immunization schedule[4]
Yellow fever	Give only when CD4+ count ≥200 cells/μL	Adult immunization schedule[4]
Herpes zoster	Give recombinant vaccine regardless of CD4+ count; discussion suggests lower humoral and cellular immune responses in persons with low CD4+ count	Berkowitz et al[5]
COVID-19	Give regardless of CD4+ count	CDC[4] and NIH COVID-19 treatment guidelines[6]
Hepatitis A	Give regardless of CD4+ count	OI guidelines[2] and adult immunization schedule[4]
Hepatitis B	Give regardless of CD4+ count; in nonresponders, can delay revaccination until CD4+ count is ≥200 cells/μL and sustained with antiretroviral therapy	OI guidelines[2]
HPV	Immune responses appear stronger among those with higher CD4+ counts and suppressed HIV viral loads	OI guidelines[2]
Influenza	Give regardless of CD4+ count	Adult immunization schedule[4]
MMR	Give only when CD4+ count is ≥200 cells/μL	Adult immunization schedule[4]
Meningococcal conjugate	Better immunogenicity if CD4+ count percentage is >15% but deferral is not specifically recommended	MacNeil et al[7]

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; HPV, human papillomavirus; MMR, measles, mumps, and rubella; NIH, National Institutes of Health; OI, opportunistic infection; PCV20, pneumococcal conjugate vaccine (protects against 20 serotypes); PPSV23, pneumococcal polysaccharide vaccine (protects against 23 serotypes); RSV, respiratory syncytial virus; Tdap, tetanus, diphtheria, and pertussis.

Immunization Practices (ACIP). The live attenuated influenza vaccine is contraindicated in PWH.[9] For those aged 65 years and older, the high-dose or adjuvanted influenza vaccine should be offered.[10] The high-dose vaccine has 4 times the antigen of standard influenza vaccines (60 μg hemagglutinin/strain vs 15 μg hemagglutinin/strain), and several studies have demonstrated a more robust antibody response to the high-dose vaccine.[11,12]

Varicella Zoster Virus

Herpes zoster, or shingles, is caused by reactivation of varicella zoster virus and is a common complication in PWH, with rates more than twice as high as an HIV-negative cohort in the Veterans Aging Cohort Study. Individuals with HIV viral suppression younger than 60 years and aged 60 years and older had higher rates of herpes zoster than individuals without HIV.[7] Current guidelines changed in 2021 to reflect the increased risk of herpes zoster for all PWH, expanding vaccination from age 50 years and older to age 18 years and older with 2 doses of the recombinant zoster vaccine at month 0 and at 2 to 6 months later. Of note, some experts recommend delaying vaccination until viral suppression is achieved on ART or until the CD4+ count is greater than 200 cells/μL.

SARS-CoV-2 Virus

Several studies have shown that PWH with COVID-19 have worse outcomes than the general population. In a large trial from the World Health Organization Global Clinical Platform with data from 24 countries, HIV was associated with a 15% increase in odds of presenting with severe COVID-19 and a 38% increase in odds of dying in the hospital.[14] Increased risk was associated with HIV even among those with viral suppression. A multicenter

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Table 2. Recommended Pneumococcal Vaccination Options for People With HIV[a]

Vaccination history	Option A	Option B	Notes
Patients aged <65 y			
Unvaccinated	PCV20	PCV15 + PPSV23 8 wk later	—
PPSV23 only	PCV20 at ≥1 y	PCV15 at ≥1 y	—
PCV13 only	PCV20 at ≥1 y	PPSV23 at ≥8 wk, repeat PPSV23 at ≥5 y	Review pneumococcal recommendations at age 65 y
PCV13 + PPSV23	PCV20 at ≥5 y	PPSV23 at ≥5 y	Review pneumococcal recommendations at age 65 y
PCV13 + PPSV23 (2 doses)	PCV20 at ≥5 y	None	Review pneumococcal recommendations at age 65 y
Patients aged 65 y and older			
Unvaccinated	PCV20	PCV15 + PPSV23 8 wk later	—
PPSV23 only	PCV20 at ≥1 y	PCV15 at ≥1 y	—
PCV13 only	PCV20 at ≥1 y	PPSV23 at ≥1 y	—
PCV13 + PPSV23 at <65 y	PCV20 at ≥5 y	PPSV23 at ≥5 y	—

[a] Option A and Option B are both approved and available for use, depending on insurance coverage and availability of vaccines.

Abbreviations: PCV13, pneumococcal conjugate vaccine (protects against 13 serotypes); PCV15, pneumococcal conjugate vaccine (protects against 15 serotypes); PCV20, pneumococcal conjugate vaccine (protects against 20 serotypes); PPSV23, pneumococcal polysaccharide vaccine (protects against 23 serotypes).

cohort study of participants predominantly from the US demonstrated worse outcomes for PWH including a composite of intensive care unit admission, ventilatory support, and death. Another study also demonstrated worse outcomes for people with a CD4+ count less than 200 cells/μL, independent of viral suppression.[15] However, studies demonstrate that vaccination protects PWH. A Canadian prospective, observational cohort study of PWH compared with controls showed that both groups had similar levels of vaccine-induced immunoglobulin G (IgG), although a lower percentage of PWH maintained IgG levels at 6 months after vaccination (92% PWH vs 99% controls).[8] In a study in South Carolina that compared PWH with a control group, PWH did not have higher rates of breakthrough infections compared with people without HIV, nor did they have higher rates of severe infection. Along with the Canadian study demonstrating lower levels of sustained immunity in PWH, this study showed that PWH had higher rates of breakthrough infection when comparing PWH with people without HIV who had not received a booster-dose vaccination.[16] The COVID-19 Treatment Guidelines Panel recommends vaccination for all PWH with any CD4+ cell count and subsequent doses on the schedule recommended by the CDC and the ACIP.[6] Individuals with advanced HIV (CD4+ count less than 200 cells/μL, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV) should follow advice for those who are moderately or severely immunocompromised.[17] PWH were included in studies for the 2 types of messenger RNA (mRNA) vaccines (Pfizer BioNTech and Moderna) and the glycoprotein vaccine (Novavax), and results showed that PWH on ART who have virologic suppression have a good immunologic response to the vaccines. For PWH, there are currently 3 options for COVID-19 vaccination, including 2 mRNA vaccines (Pfizer BioNTech and Moderna) and the glycoprotein vaccine (Novavax). The most updated guidance on COVID-19 immunization with any of the recommended vaccines can be found at the CDC website.[6]

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Table 3. Recommended Immunizations for People With HIV, by Age[a]

Disease(s)	Vaccination recommendation by age			
	19-26 y	27-59 y	60-64 y	≥65 y
Influenza	1 dose of influenza vaccine annually			1 dose (high dose) annually
Tdap	1 dose of Tdap, then Td or Tdap booster every 10 y			
Varicella infection	2 doses, 3 mo apart (if CD4+ count is ≥200 cells/μL and no immunity to varicella virus)			
HPV	3 doses (0, 2, and 6 mo)	27-45 y[b]	—	—
Herpes zoster infection	Recombinant vaccine: 2 doses at 0 and 2-6 mo			
MMR	1 or 2 doses (if CD4+ count is ≥200 cells/μL and no immunity to MMR viruses)			—
Pneumococcal disease	See Table 2			
Hepatitis A	2 or 3 doses depending on the vaccine, at 0 and 6-18 mo. Check HAVAb 1-2 mo after.			
Hepatitis B	2 or 3 doses depending on the vaccine. Check HBsAb 1-2 mo after.			
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 guidelines[3]).			
Mpox	2 doses separated by 28 days for those at risk[c]			
RSV	—	—	1 dose[d]	
COVID-19	The 2023-2024 formulations of the COVID-19 vaccine are available from several manufacturers. See CDC guidance.[8]			

[a] Immunizations should be given after assessment of age, presence of immunity to the pathogen (for hepatitis A and B), and CD4+ counts. Live replicating vaccines, including MMR, varicella, and yellow fever, should not be given if CD4+ count is less than 200 cells/μL. The oral live influenza vaccines are contraindicated in all people with HIV. Recommendations current as of October 2023.

[b] HPV 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.

[c] Individuals at risk for mpox include those who may have contact with mpox through workplace or sexual exposure.

[d] RSV vaccination is recommended for those with cardiopulmonary disease, kidney disorders, liver disorders, neurologic or neuromuscular conditions, hematologic disorders, diabetes mellitus, or moderate or severe immune compromise (attributable to either 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 practitioner determines might increase the risk for severe respiratory disease.

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; RSV, respiratory syncytial virus; Td, tetanus and diptheria; Tdap, tetanus, diptheria, and pertussis.

Respiratory Syncytial Virus

RSV is more likely to cause hospitalization, lower respiratory tract disease, and death in older adults, with 60,000 to 160,000 hospitalizations and 6000 to 10,000 deaths in the US in those aged 65 years and older. There are 2 types of RSV vaccines licensed for use in the US: RSVPreF3 (Arexvy) and RSVpreF (Abrysvo), both recombinant prefusion F protein vaccines. The ACIP recommends that either RSV vaccine may be given as 1 dose with shared clinical decision-making for adults aged 60 years and older who are at the highest risk. Additionally, during RSV season, the ACIP recommends that pregnant persons at 32 to 36 weeks of gestation be vaccinated with 1 dose of RSVpreF.[18] Individuals at the highest risk for severe lower respiratory tract RSV disease include those with chronic lung disease, cardiovascular disease, moderate or severe immunocompromise, diabetes, neurologic or neuromuscular conditions, kidney disorders, liver disorders, or hematologic disorders; individuals who are frail; those of advanced age; and those who are residents of long-term care facilities.[19] A study that evaluated data from RSV-associated hospitalizations found obesity as a risk factor for hospitalization.[20] Given the risk for increased severity of RSV infection in those who are immunocompromised, it would be reasonable to offer this vaccine to PWH aged 60 years and older, especially those with advanced HIV and other comorbidities.

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Table 4. Vaccines for Travel for People With HIV

Vaccine	Location	Notes
Meningococcus	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 (for individuals with CD4+ count ≥200 cells/μL)	—
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	—
Chikungunya	Parts of Central and South America, Mexico, parts of Africa and Asia	Travelers to areas of outbreaks should be vaccinated, as well as those traveling to areas with transmission in the last 5 years[34]

Currently, there are no specific guidelines for the use of RSV vaccines in PWH. At this time, there is insufficient evidence to know if additional doses of the vaccine should be recommended.

Neither the RSVPreF3 nor the RSVpreF vaccine had an increased incidence of serious adverse events (AEs) compared with placebo, and each prevented 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 in people with RSV vaccination, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and acute central nervous system inflammation. The RSVPreF3 and RSVpreF each had 3 cases of inflammatory neurologic events out of 17,922 and 20,255 participants, respectively, demonstrating a low incidence of these events. Both vaccine studies had slightly increased episodes of atrial fibrillation, which occurred in 10 participants in each of the vaccine groups and 4 participants in each of the control arms.[21,22] It is unclear if there is a relationship between the vaccine and these events, but more information may come from postmarketing AE reporting. This information can be used to inform a discussion of the risks and benefits of this vaccine.

Streptococcus pneumoniae

PWH are at higher risk for invasive pneumococcal infections than the general population, including those individuals on ART.[23,24] Several new pneumococcal vaccines have recently become available, substantially changing the recommendations for vaccination. A study demonstrated immunogenicity and safety of the 15-valent pneumococcal conjugate vaccine (PCV15) followed by 23-valent pneumococcal polysaccharide (PPSV23) vaccine in PWH.[25] 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.

PWH without a history of vaccination can be vaccinated with either PCV20 alone or a combination of PCV15 with PPSV23 administered 8 weeks later. Options are available for PWH younger than 65 years of age (Table 3). For those aged 65 years and older, the options are slightly simplified, with only 1 vaccine dose recommended after that age.

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Hepatitis A Virus

HAV is transmitted through fecal-oral routes. PWH are at high risk for severe disease from HAV infection. Person-to-person transmission has been documented in the US. Vaccination is recommended for all PWH aged 1 year and older.[26] Vaccination for hepatitis A is recommended at 0 and 6 to 12 months or in combination with hepatitis B vaccination (Twinrix) at 0, 1, and 6 months. Antibody response should be assessed 1 to 2 months after vaccination. If there is incomplete response in the setting of low CD4+ cell count, repeat vaccination should be offered when the CD4+ count rises to more than 200 cells/μL.[2]

Hepatitis B Virus

Hepatitis B is a common coinfection in PWH who are also at increased risk for developing chronic hepatitis B. The incidence of hepatitis B has been declining over time due to hepatitis B vaccination as well as suppression of chronic infection with antiviral treatment. Current recommendations are for initial vaccination to be with

The incidence of hepatitis B has been declining over time due to hepatitis B vaccination as well as suppression of chronic infection

1 of 3 HBV vaccines. The first option is the recombinant HBV surface antigen vaccine conjugated to an adjuvant toll-like receptor 9 (HBCpG, Heplisav-B) given at 0 and 1 month. The second is a double-dose recombinant hepatitis B vaccine at 0, 1, and 6 months, and the third option is the combined hepatitis A and hepatitis B vaccine (Twinrix) at 0, 1, and 6 months. The combination option may have lower immunogenicity given the lower dose of HBV antigen. Vaccinated individuals should have immunity checked with HBV surface antibody 1 to 2 months after vaccination. If there is inadequate response to the initial series (HBV surface antibody <10 mIU/mL), repeat vaccination is recommended. A recent studiy in individuals with inadequate response to initial hepatitis B vaccination has demonstrated superiority of repeat vaccination with HBcPG (Heplisav-B) 2 or 3 doses compared with recombinant hepatitis B vaccination.[27] The US Department of Health and Human Services (DHHS) Opportunistic Infection Guidelines recommend that HBV vaccination not be deferred based on CD4+ count, but if there is a lack of response to initial vaccination in the setting of a CD4+ count less than 200 cells/μL, repeat vaccination can be delayed until immune recovery.[2]

Individuals with HBV core antibody and no evidence of chronic infection or immunity should receive a standard-dose vaccination with a check in 1 to 2 months of quantitative HBV surface antibody (HBsAb) titer. If the HBsAb titer is less than 100 mIU/mL, the individual should receive complete vaccination.[2]

Human Papillomavirus

HPV infection is very common in the US, with approximately 80% of people having had HPV infection at some time. HPV causes almost 47,000 cancers every year in the US, including in the cervix, vagina, vulva, anus, oropharynx, and penis. Oropharyngeal cancer is the most common HPV-related cancer in men and cervical cancer the most common HPV-related cancer in women.[28] Rates of anal cancer in some PWH are more than 50 times the rates seen in the general population and all PWH are at higher risk for anal cancer.[29] Cervical cancer is the fourth most common cancer worldwide and is more common in PWH. Approximately 6% of cervical cancers are diagnosed in PWH.[30] HPV vaccination before exposure to the virus can prevent more than 90% of HPV-related cancers.

HPV vaccination for PWH is recommended in 3 doses at 0, 1, and 6 months at age 11 to 12 years, starting as early as age 9 years. The vaccine is most effective in preventing HPV infection 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

Rates of anal cancer in some PWH are more than 50 times the rates seen in the general population and all PWH are at higher risk for anal cancer

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 offered only up to age 26 years, but in 2019, the ACIP expanded this recommendation for individuals at risk up to age 45 years

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with shared clinical decision-making with the patient and the clinician.[31] Vaccination from 27 to 45 years of age 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. There is no current evidence suggesting that HPV vaccination reduces the risk of recurrent HPV-related disease in PWH; however, studies of therapeutic vaccines to treat HPV infection in this population are ongoing.[32,33]

Neisseria meningitidis

Although meningococcal disease is not common, there is a 5- to 13-fold higher risk in PWH than in the general population, with the highest risk in individuals with a low CD4+ cell count or with viremia.[7] In 2016, the meningococcal polysaccharide conjugate vaccines (either formulation MenACWY-CRM [Menveo] or MenACWY-TT [MenQuadfi]) were recommended for PWH in a 2-dose series at least 8 weeks apart with a booster every 5 years. A third formulation, MenACWY-D (Menactra), is no longer available. The meningococcal ACWY vaccines are interchangeable in adults.

Meningococcal B vaccine is recommended for some PWH, including those aged 16 to 23 years (preferred 16-18 years), those at risk (living in close quarters, those with asplenia), and during outbreaks. Two meningococcal B vaccines are available, MenB-4C (Bexsero; 2-dose series given at 0 and 1 month) and MenB-FHbp (Trumenba; PWH should receive the 3-dose series given at 0, 1 to 2, and 6 months, and not the 2-dose option). The meningococcal B vaccines are not interchangeable. The Food and Drug Administration approved a pentavalent A, B, C, W, and Y meningococcal vaccine (using the Men-FHbp or non-outer membrane vesicle [OMV]-based meningococcal B), which is available for persons ages 10 to 25 years, and its use in PWH has not been defined.

Recently, there has been investigation into whether meningococcal group B vaccine targeting the OMV could reduce the incidence of gonorrhea infection, given that the OMV is found on *Neisseria meningitidis* and on *Neisseria gonorrhoeae*. Retrospective population studies linking vaccination records to infections of gonorrhea in New Zealand and in the US showed between 31% and 40% vaccine effectiveness against gonorrhea after use of MenB-4C meningococcal B vaccine.[35,36] A study in Oregon colleges compared the use of 2 meningococcal B vaccines; MenB-4C is OMV based (Bexsero) and MenB-FHbp (Trumenba) is not. The OMV-based vaccine was 47% effective in preventing gonorrhea in this population.[37] Although these data suggest some protection by MenB-4C against gonorrhea, further prospective, randomized studies in larger populations are warranted to assess this effect. One prospective study, DOXYVAC (Combined Prevention of Sexually Transmitted Infections in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Preexposure Prophylaxis), demonstrated a trend toward MenB-4C protecting against gonorrhea, although the results did not reach statistical significance.[38]

Mpox

A worldwide epidemic of mpox peaked in the summer of 2022, with ongoing cases seen subsequently, though not at the levels of 2022. A CDC analysis of 103 individuals hospitalized with mpox showed that 90 (87%) of these individuals had HIV and 88% of those had a CD4+ count less than 200 cells/μL.[39] Twenty of 22 persons who died had HIV and none of those were on ART. PWH, especially those without viral suppression and low CD4+ cell counts, are at risk for severe disease from mpox. The ACIP recommends the mpox vaccine with the live, nonreplicating vaccinia vaccine (Modified Vaccinia Ankara–Bavaria Nordic, JYNNEOS) with 2 doses 4 weeks apart for individuals with HIV who are at risk for mpox exposure or request vaccination. If the second dose is delayed, it can be given as soon as possible without repeating the series. The vaccine can also be used as postexposure prophylaxis within 4 to 14 days after known exposure to someone with mpox, including sex in the past 2 weeks with someone with mpox. Immunogenicity to the live nonreplicating mpox vaccine is lower in PWH who are not virologically suppressed or with CD4+ counts less than 100 cells/μL. Live replicating vaccinia virus (ACAM2000) is contraindicated in PWH.

The mpox vaccine can be used as postexposure prophylaxis within 4 to 14 days after known exposure to someone with mpox

This article was based on the presentation, Routine and Special Immunizations for People With HIV, *by Steven C. Johnson, MD, in August 2023. The presentation webcast can be viewed at https://www.youtube.com/watch?v=_7yT2RW-5wY*

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Invited Review

Messenger RNA Vaccine Technology: Success for SARS-CoV-2 and Prospects for an HIV-1 Vaccine

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Abstract: *Over the past several years, messenger RNA (mRNA) vaccine has evolved from a term familiar only to vaccine scientists into one easily recognized by much of the general population. This change occurred because of the remarkable success of effective and safe mRNA vaccines during the COVID-19 pandemic that saved countless lives. Although mRNA vaccine technology has a clear use for combating future emerging diseases, its role in fighting currently known pathogens, such as HIV-1, is not well defined. This review summarizes mRNA vaccine technology, highlighting its success during the COVID-19 pandemic. It then addresses past and current efforts to develop a vaccine for HIV-1, including how mRNA vaccine technology has created opportunities in the ongoing search for an effective HIV-1 vaccine.*

Keywords: COVID-19, vaccines, mRNA vaccine technology, HIV vaccine, SARS-CoV-2, HIV

Scientific Breakthroughs Key to mRNA Vaccine Technology Before COVID-19

Messenger RNA (mRNA) was first identified in 1961 as an unstable molecule that carries information between genes and ribosomes.[1] Over time, it was discovered that these molecules were found in all cells and were necessary for protein synthesis. Eventually, scientists realized that mRNA could be used to synthesize proteins from viruses and other infectious agents and thus be harnessed as a potential vaccine platform. In simple terms, mRNA vaccines work through the injection of a synthetic mRNA molecule that encodes a specific target protein. Once engulfed by the host immune cells, the mRNA molecules are translated into intracellular proteins, with subsequent presentation of the desired antigen, ultimately generating a targeted immune response.

Thirty years after its discovery, mRNA was first tested as a potential vaccine in animal models. The first mRNA vaccine showed the generation of a CD8+ T-cell response, or cytolytic T-cell response, in mice through the use of liposomes containing mRNA that encoded influenza proteins.[2] A few years later, another group found that mRNA vaccine technology could be used to elicit antibodies directed toward cancer antigens.[3] These studies lend credence to the potential of the mRNA vaccine platform.

Since these first studies were conducted, several important discoveries have allowed mRNA vaccines to become more popular within the scientific community. These advances are summarized in Figure 1. First, the use of cell-free technology in an in vitro process has made the production of mRNA vaccines more efficient. Another important breakthrough was the incorporation of lipid nanoparticles that surrounded the mRNA molecule in the vaccine, allowing for decreased degradation and enhanced delivery. These lipid nanoparticles are composed of ionizable lipids, improving the safety and extending the circulation time of the mRNA vaccine.[4] Following the initial discovery of lipid nanoparticles, new candidate ionizable lipids were examined through large-scale library testing. The result was the discovery of further optimized lipids, such as SM-102 (used in the Moderna COVID-19 mRNA vaccine, or mRNA-1273)[5] and ALC-0315 (used in the Pfizer-BioNTech COVID-19 mRNA vaccine, or BNT162b2).[6,7] Another important discovery was the identification of the benefits of mRNA modifications such as using modified mRNA nucleosides like pseudouridine. The immune system has evolved pattern recognition receptors (PRRs) that can recognize uridine-rich regions of mRNA. By incorporating pseudouridine into the vaccine, researchers were able to prevent PRR recognition, leading to slower degradation of the mRNA molecule.[8] The addition of pseudouridine

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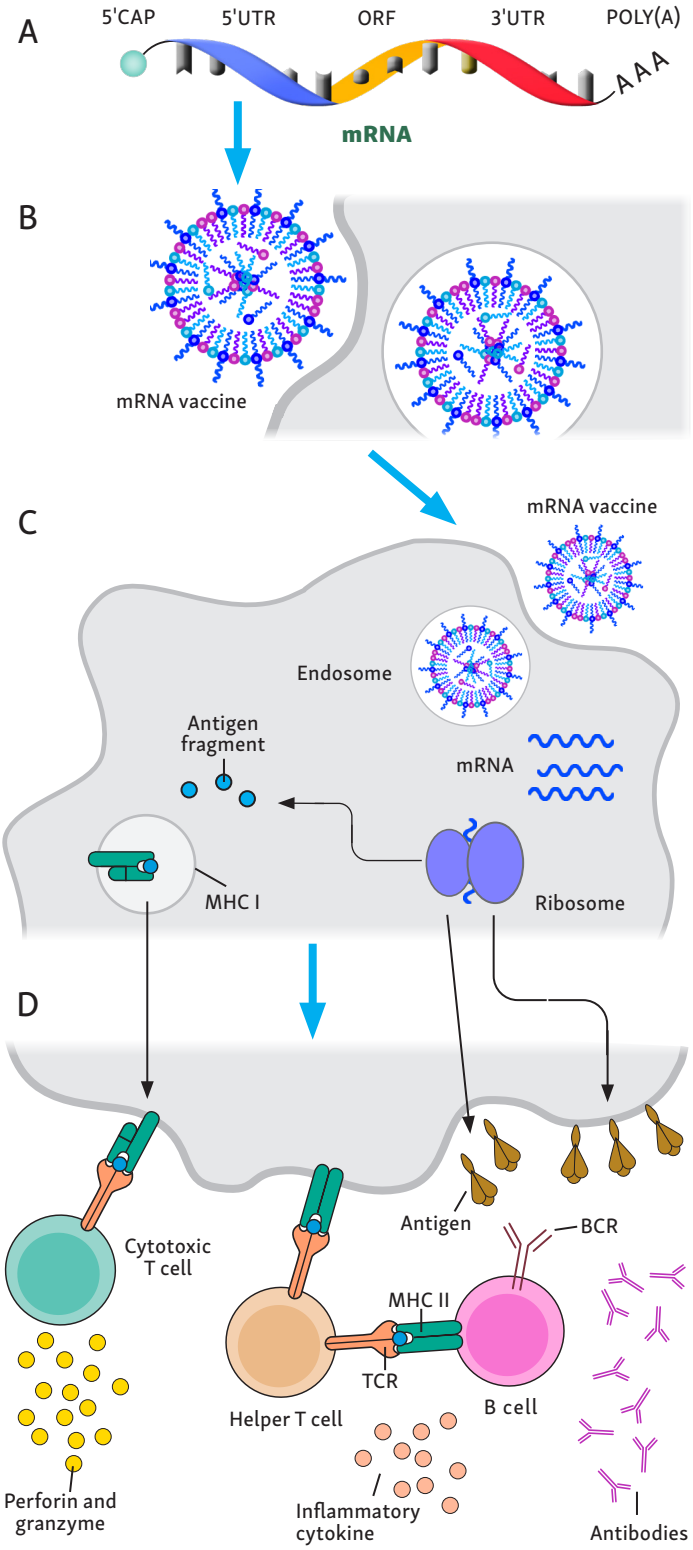

was first described by Karikó and Weissman and led to the pair receiving the 2023 Nobel Prize in Physiology or Medicine.[9-11] Both the Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines included pseudouridine.[4] Another major advance in the vaccine field was the use of fusion glycoproteins for respiratory syncytial virus vaccine, which was found to generate improved antibody responses in vaccine recipients.[12] All the COVID-19 vaccines (with the exception of the AstraZeneca vaccine) employed a similar fusion-stabilizing mutation in the spike protein that has been demonstrated in preclinical models to improve the induction of neutralizing antibodies.[13]

Over time, it was found that mRNA vaccines have advantages over other vaccine platforms. Importantly, mRNA vaccines can be rapidly developed and tailored to new diseases. mRNA vaccines are synthesized using an in vitro transcription process, in which a DNA template is transcribed into mRNA. Once an entity establishes this mRNA vaccine platform, it can easily exchange the open reading frame, or the section of the DNA template that encodes the desired antigen, for a sequence that encodes a new target.[14] This strategy can be used to target emerging infectious diseases much more efficiently than other vaccine platforms, resulting in faster vaccine development.[14,15] mRNA vaccines are also very immunogenic and have been found to generate robust antibody and CD4+ and CD8+ T-cell responses, as opposed to inactivated or subunit protein vaccines, which will generate responses biased to the humoral immune system.[14] Although recombinant virus vaccines can generate strong immune responses, mRNA vaccines may offer improved safety and fewer production challenges.[16,17] Also, nucleic acid vaccines, such as mRNA and DNA vaccines, offer improved flexibility in the manufacturing processes, as mentioned previously. However, DNA vaccines require entering the nucleus of a cell to initiate antigen production. Historically, DNA vaccines have been less immunogenic than mRNA vaccines.

Because of the advantages that mRNA vaccines offer, as well as numerous studies showing their safety and immunogenicity in preclinical animal models, researchers began advancing mRNA vaccines to clinical trials in humans. In 2015, one of the first human phase 1 clinical

Figure 1. Advances in Messenger RNA Vaccine Technology. Numerous advances have led to the optimized mRNA vaccine technology used today. (A) Improvements in in vitro transcription/cell-free production of mRNA vaccine technology have made vaccine synthesis easier and cost effective. (B) The use of optimized lipid nanoparticles and mRNA modifications, including pseudouridine, has enhanced RNA stability and reduced innate immune breakdown. (C) These advances have resulted in improved uptake of mRNA molecules, leading to ribosomal synthesis of antigen. (D) The ultimate result will be antigen presentation to B cells, leading to antibody responses and antigen fragment presentation to T cells.
Abbreviations: BCR, B-cell receptor; MHC, major histocompatibility complex; mRNA, messenger RNA; TCR, T-cell receptor.

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trials targeted the rabies virus.[18] Overall, this vaccine generated strong antibody responses with a tolerable safety profile. An mRNA vaccine targeting H10N8 and H7N9 influenza viruses demonstrated antibody seroconversion and tolerability in humans.[19] After these successes, groups began preparing to use mRNA vaccine technology but were waiting for the right moment to begin large-scale production.

Vaccine Successes in the COVID-19 Pandemic

In December 2019, health officials began to report an increasing number of pneumonia infections in Wuhan, China.[20] As the weeks progressed, it became clear that the new virus causing these infections, later named SARS-CoV-2, posed a substantial health risk. Like its predecessor, the severe acute respiratory syndrome (SARS) virus, the new virus binds to the angiotensin-converting enzyme-2 receptor, but it was ultimately found to be much more transmissible, infecting hundreds of millions and spreading globally. Some of the latest estimates from the World Health Organization indicate that there have been 770 million confirmed infections and approximately 7 million deaths from COVID-19,[21] although many experts believe these are likely underestimates given the limitations of identifying cases and reporting these statistics.

Although SARS-CoV-2 had a worldwide impact, the quick development and deployment of vaccines targeting the virus saved countless lives. One model estimates that COVID-19 vaccines saved 14.4 million lives during the second year of the pandemic alone.[22] Early collaboration within the scientific community was key to combating this new disease. Such teamwork included the release of the genomic sequence on January 10, 2020, just weeks into the pandemic.[23,24] Collaborative relationships were formed as clinical trials testing new therapeutics were started by groups around the world. By the end of 2020, there were numerous medications[25-27] and 2 different vaccines[28,29] that had been granted emergency use authorization (EUA) by the US Food and Drug Administration (FDA).

One model estimates that COVID-19 vaccines saved 14.4 million lives during the second year of the pandemic alone

Although speed was a priority for the COVID-19 vaccine during a worldwide pandemic, it was important that no shortcuts were taken regarding safety. Numerous decisions and factors led to the rapid development of these vaccines. For example, many phase 1 and phase 2 trials were combined and clinical trialists began designing the phase 3 trial while these earlier trials were ongoing. The researchers also recruited large numbers of study participants and were fortunate that the trials were conducted during periods of relatively high infection rates. Additionally, SARS-CoV-2 proved to be not as formidable a pathogen for vaccine-induced protection as some highly variable viruses such as HIV-1 and hepatitis C.

Although speed was a priority for the COVID-19 vaccine during a worldwide pandemic, it was important that no shortcuts were taken regarding safety

There are now numerous vaccines targeting SARS-CoV-2. This review focuses primarily on select vaccines that were given monetary support from the US government during the early stages of the pandemic: the Moderna, AstraZeneca, Janssen, Novavax, and Sanofi vaccines. Although the Pfizer-BioNTech vaccine did not receive direct support, the US government agreed to buy it, assuming that it would be efficacious. A summary of these vaccines is shown in the Table. The Pfizer-BioNTech and Moderna vaccines used mRNA vaccine technology.[28,29] The AstraZeneca and Janssen vaccines used recombinant adenoviral vector vaccine technology, which involved using a reengineered attenuated virus to deliver SARS-CoV-2 viral DNA that was subsequently translated into proteins and presented to the host immune system.[30,31] The Novavax and Sanofi products were protein-based vaccines that included a manufactured version of the SARS-CoV-2 spike protein.[32,33] Notably, the Sanofi vaccine did not show efficacy in SARS-CoV-2-naive participants, potentially because of the new SARS-CoV-2 variants emerging. As stated previously, these vaccine trials went through the necessary regulatory processes to ensure patient safety. Importantly, all the vaccines elicited close to 100% protection against severe infection compared with unvaccinated control groups. It should be noted that the original Janssen vaccine trial used only a single dose and the vaccine was initially less

Table. Overview of SARS-CoV-2 Vaccines

Vaccine manufacturer	Vaccine type	Dose, regimen	Protection from severe infection, %	Protection from infection, % (95% CI)	Date of approval/EUA
Pfizer/BioNTech	mRNA	2 doses, 21 days apart	100	95 (90.3-97.6)	December 11, 2020
Moderna	mRNA	2 doses, 28 days apart	100	94.1 (89.3-96.8)	December 18, 2020
AstraZeneca	Viral vector	2 doses, 28 days apart	100	70.4 (54.8-80.6)	December 30, 2020[c]
Janssen	Viral vector	1 dose	85[b]	66.1 (55.0-74.8)[b]	February 26, 2021
Novavax	Recombinant protein	2 doses, 21 days apart	100	89.3 (75.2-95.4)	July 13, 2022
Sanofi[c]	Recombinant protein	2 doses, 21 days apart	99	64.7 (46.6-77.2)	November 10, 2022[d]

[a] The AstraZeneca vaccine was first approved in Europe and the company never sought EUA from the US Food and Drug Administration.

[b] The Janssen vaccine was first approved as a single dose on February 27, 2021; a double-dose regimen with improved efficacy was later approved. This approval was withdrawn in May 2023, and Janssen is no longer manufacturing the vaccine.

[c] The Sanofi vaccine did not show efficacy in SARS-CoV-2–naive participants.

[d] The Sanofi vaccine was approved in Europe and never received approval or EUA from the US Food and Drug Administration.

Abbreviations: EUA, emergency use authorization; mRNA, messenger RNA.

protective against severe disease at 85%; however, an additional trial that tested this vaccine with a 2-dose regimen found a level of protection similar to those of the other vaccines tested.[34] Long-term data have shown that COVID-19 vaccines are very effective at preventing mortality and severe infection (Figures 2 and 3). On September 22, 2021, the FDA granted additional EUA to the Pfizer-BioNTech, Moderna, and Novavax COVID-19 booster vaccines. As shown in Figure 3, the latest data indicate that vaccinations and these boosters continue to help prevent mortality and severe complications.[36]

Although almost all of these COVID-19 vaccines generated a similar degree of protection, there were clear advantages to the mRNA vaccines. The most discussed advantage was the speed and efficiency of the manufacturing process, partly explaining how these vaccines were able to receive EUA from the FDA less than a year after being created. The Pfizer-BioNTech and Moderna mRNA vaccines received this authorization a few months before the Janssen vaccine and a year and a half before the Novavax vaccine. The AstraZeneca vaccine did gain approval only a few weeks after the Pfizer-BioNTech and Moderna vaccines; however, this approval was granted primarily in England and Europe, which have different regulatory processes from those in the US. One example of the difficulties in using other vaccine platforms is evident with the Sanofi vaccine, which was stalled because of a low protein concentration in the first formulation of the vaccine.[37] Additionally, the 2 mRNA vaccines appeared to generate mildly improved initial protection from infection compared with the AstraZeneca and Janssen vaccines (see Table).[38] It is well documented that protection from infection decreases over time because of a variety of factors, including waning host immune responses and viral div-ersity of SARS-CoV-2. In short, these COVID-19 vaccines elicited a protective immune response against SARS-CoV-2, and the development of these vaccines in less than a year is a testament to the commitment of the scientific community.

Long-term data have shown that COVID-19 vaccines are very effective at preventing mortality and severe infection

Difficulties in Creating an HIV-1 Vaccine

In contrast to the SARS-CoV-2 experience, efforts to create an effective vaccine targeting HIV-1 have been unsuccessful, despite decades of research and more than 100 clinical trials. The first HIV-1 vaccine clinical trials performed were aimed at generating antibody responses targeting the surface glycoprotein of HIV-1, known as the HIV-1 envelope (Env).[39,40] These early HIV-1 vaccines did induce binding antibody responses, but these antibodies only neutralized a few HIV-1 strains and did not prevent infection in humans exposed to more diverse viral strains, in stark contrast to the COVID-19 vaccines, which induced potent neutralizing antibodies targeting the spike protein of SARS-CoV-2. After these early failures, the strategy changed and the next HIV-1 vaccines targeted intracellular proteins of HIV-1. The hope was that such vaccines would generate CD8+ T-cell responses that might not prevent infection but could protect against HIV-1 progression and AIDS.[41,42] Although such findings were demonstrated in preclinical nonhuman primate models,[43] the human efficacy study that tested this concept failed to demonstrate protection against infection or an impact on plasma HIV RNA level in those infected. After these clinical trials, the next study conducted was the RV144 (Thai Phase 3 clinical trial), which showed modest efficacy (31.2% at 42 months) after statistical adjustments and may represent the most successful HIV-1 vaccine trial to date.[44] This vaccine generated both antibody and CD4+ T-cell responses toward HIV-1, and it was later found that increased levels of protection correlated with antibodies specific for a region of Env known as the V1V2 loop.[44] Despite this promising result, a more recent trial performed in South Africa known as HVTN (HIV Vaccine Trials Network) 702 was intended to build on these results using a vaccine strategy similar to that of RV144, but ultimately no efficacy was demonstrated.[45]

There are numerous reasons why researchers have had such difficulties with creating an effective HIV-1 vaccine. HIV-1 vaccines generate antibody responses, but, in contrast to other viral vaccines such as those targeting COVID-19, the antibodies are poorly neutralizing and do not prevent HIV-1 infection. This phenomenon is due at least in part to the remarkable viral diversity of HIV-1.[46,47] As these mutations arise over the course of chronic infection within a host, specific strains will have the ability to undergo immune escape and evade the host immune response. Supporting this theory is that numerous HIV-1 mutations have been proven to represent escape from antibody and CD8+ T-cell responses.[48,49] Our group has also shown that HIV-1 can mutate, or undergo adaptation, in response to CD4+ T-cell responses,[50] and that these HIV-1 adaptations to

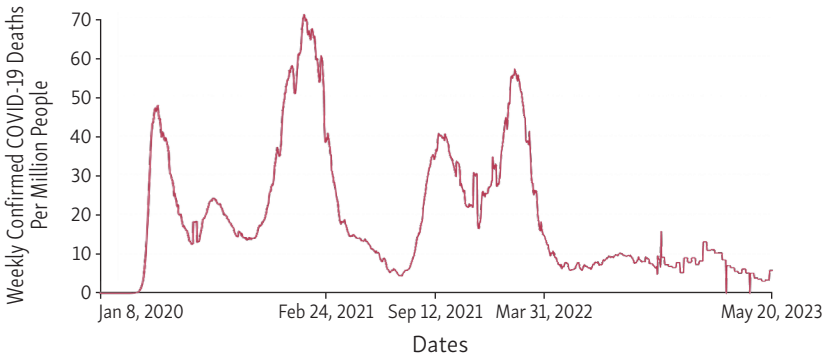

Figure 2. Weekly Confirmed COVID-19 Deaths Per Million People in the US. Weekly confirmed deaths refer to the cumulative number of confirmed deaths over the previous week. Due to varying protocols and challenges in the attribution of the cause of death, the number of confirmed deaths may not accurately represent the true number of deaths caused by COVID-19. Data from the World Health Organization COVID-19 Dashboard, figure adapted with permission from Our World in Data.[35]

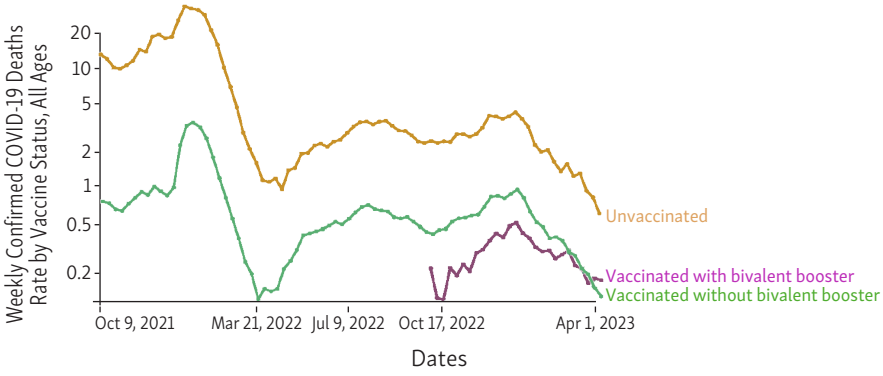

Figure 3. Weekly COVID-19 Death Rate By Vaccination Status in the US, All Ages. Death rates are calculated as the number of deaths in each group, divided by the total number of people in this group. This is given per 100,000 people. Data from the Centers for Disease Control and Prevention , Vaccine Breakthrough/Surveillance and Analytics Team, figure adapted with permission from Our World in Data.[35] Note: The mortality rate for the "all ages" group is age standardized to account for the different vaccination rates of older and younger people.

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CD4+ and CD8+ T-cell responses can affect HIV-1 vaccine responses.[51,52] The ability of HIV-1 to mutate quickly is also the reason the virus develops resistance to certain drugs, resulting in the clinical treatment of HIV-1 with a cocktail of 3 antiretroviral medications.[53] An additional hurdle is that after infection, HIV-1 integrates into the host genome and causes latent infection. As a result, to ultimately be effective, an HIV-1 vaccine will likely need to completely prevent infection, as opposed to preventing only symptomatic infection or severe infection, as with vaccines for other viruses. As a result, the task of creating an effective vaccine for HIV-1 poses one of the greatest challenges vaccine researchers have faced.

However, there is reason for hope. Two recent studies, collectively referred to as the AMP (antibody-mediated protection) study, investigated whether protection from HIV-1 infection could be achieved via passive immunization of an HIV-specific antibody.[54] Unlike traditional vaccination strategies that rely on the host immune system to produce antibodies, recipients in this study were passively immunized with an antibody targeting Env. This antibody was the broadly neutralizing antibody (bNAb) called VRC01, which has been shown to target numerous strains of HIV-1.[54] Unfortunately, no overall protection against infection following bNAb injection was demonstrated. However, analyses of the results showed that participants receiving this antibody were less likely to be infected with VRC01-sensitive HIV-1 strains, suggesting that the bNAb was providing some level of protection against certain strains of HIV-1. This is an important finding and suggests that for future HIV-1 vaccines to be effective, the immune response would likely need to generate multiple bNAbs with complementary mechanisms of action, similar to what is achieved with combination antiretroviral therapy for HIV-1 treatment. Follow-up studies are being discussed that would confirm this hypothesis by investigating whether passive immunization with multiple bNAbs could prevent HIV-1 infection.

Promising New HIV-1 Vaccine Strategies and the Potential Role of mRNA Vaccine Technology

Although we now have a better idea of what may be needed, the task of creating an HIV-1 vaccine remains daunting. bNAbs are typically produced in only a minority of individuals after years of chronic HIV-1 infection. To generate HIV-specific bNAbs, a vaccine would need to mimic the process of what happens over years of HIV-1 infection. This approach has led to one of the most promising strategies, which is to create bNAbs by sequential immunization, involving a vaccine with 3 distinct steps to mirror the development of bNAb-producing B cells (Figure 4). The first step is called "priming," which involves germline targeting and expanding the first B-cell precursors. Although these B cells do not have neutralizing antibody capacity, they do have the potential to produce HIV-1 bNAbs if subsequently boosted with the correct antigen. This boosting, or second step, will involve "shepherding" these precursors through B-cell development, and the final step, termed "polishing," will mature these cells into bNAb-producing plasma cells. Recent

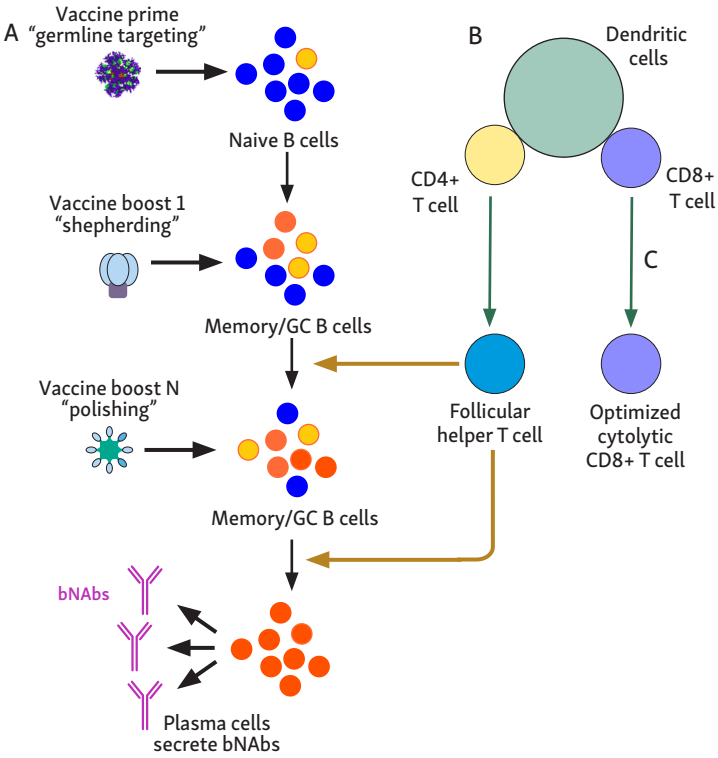

Figure 4. Strategies for Future HIV-1 Vaccine Trials. A successful HIV-1 vaccine will likely need to use a multicomponent approach. (A) The most promising strategy to date involves sequential immunization, which uses a 3-step approach of priming/germline targeting, then shepherding, and finally polishing to generate bNAb-secreting plasma cells. (B) In addition, the HIV vaccine would involve dendritic cell presentation of antigen to both CD4+ and CD8+ T cells. Optimal CD4+ T cells would form robust T-follicular helper-cell responses that assist in shepherding and polishing the B-cell response. (C) Optimal CD8+ T-cell responses, potentially using human leukocyte antigen (HLA)-E–specific responses, would then be able to assist in killing any virally infected cell. Abbreviations: GC, germinal center; bNAb, broadly neutralizing antibody.

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studies have been successful in priming naive B cells in order to expand B-cell precursors with the potential to specifically produce VRC01 bNAbs.[55] Ongoing research is focused on using this strategy or a similar framework to expand other B-cell precursors capable of targeting other regions of Env. Although many bNAbs target the CD4 binding site of HIV-1 Env, several other bNAb targets have been identified, including V2 apex, V3 glycan, fusion peptide, and the membrane-proximal external region. Recent reviews have discussed these findings in detail.[56] Ultimately, based on the findings from the AMP study, an HIV-1 vaccine may be able to elicit protection if it can generate bNAbs that target several complementary HIV-1 Env sites.

Although B-cell and antibody generation has been a recent focus in the HIV-1 vaccine field, optimization of T-cell responses may also play an important role in HIV-1 vaccine design. A specific subset of CD4+ T cells known as T follicular helper (Tfh) cells are found in the germinal centers of lymph nodes and may be crucial to maturation of B-cell precursors into bNAb-producing plasma cells. Supporting this idea is that the RV144 trial indicated a correlation between polyfunctional Env-specific CD4+ T cells and decreased risk of infection.[57] More recent studies have shown that induction of strong CD4+ Tfh cell response was required to induce bNAbs.[58,59] Future research should investigate adjuvants and other vaccine strategies capable of stimulating Tfh-dominant responses.

Future research should investgate adjuvants and other vaccine strategies capable of stimulating Tfh-dominant responses

Additionally, it may be possible to improve HIV-1 vaccine responses by harnessing CD8+ T cells. Although previous HIV-1 vaccines aimed at generating CD8+ T-cell responses were shown to be ineffective at providing protection from infection, there is evidence to suggest that CD8+ T cells can play a role in HIV-1 vaccines. In HVTN 505, a previous HIV-1 vaccine efficacy trial, CD8+ T-cell responses targeting Env correlated with decreased risk of infection.[60] Also, there has been promise in investigating HLA-E–specific CD8+ T-cell responses. These responses were first described with a cytomegalovirus viral vector vaccine that induced CD8+ T cells restricted by the HLA-E analogue in simian immunodeficiency virus animal models.[61] Such responses were shown to be essential to protect against simian immunodeficiency virus infection.[62] These preclinical animal vaccine trials are encouraging, and human clinical studies are currently ongoing. However, the cytomegalovirus viral vector will be a live attenuated vaccine, with greater challenges in manufacturing and potentially increased adverse effects.

Although many HIV-1 vaccine studies have used other vaccine types, mRNA vaccine technology can play a crucial role in the ongoing search for an effective HIV-1 vaccine. Many experts believe that mRNA vaccines are optimal for testing new vaccine strategies because they can deliver complex multipart immunogens. An effective HIV-1 vaccine will likely need to generate complementary bNAbs while also stimulating Tfh and CD8+ T-cell responses. This broad approach will require investigation of complementary strategies. mRNA vaccines provide a good platform because they generate strong T-cell and antibody responses. Because various mRNA vaccines can be created quickly, these new strategies could be investigated more efficiently using the mRNA platform, providing the field with answers regarding how to optimize the next generation of vaccines. mRNA vaccines may also produce an improved immune response compared with other vaccine platforms. For instance, previous studies have shown that lipid nanoparticle-enclosed mRNA can induce potent Tfh responses.[63,64] Ongoing studies are investigating whether Env trimer nanoparticle multimers can be formed using the mRNA platform.[65,66] Inclusion of the transmembrane domain of HIV-1 Env in mRNA vaccines could lead to the generation of a membrane-bound Env that may prove to be beneficial, as it will lead to presentation to the immune system in its more

Although previous HIV-1 vaccines aimed at generating CD8+ T-cell responses were shown to be ineffective at providing protection from infection, there is evidence to suggest that CD8+ T cells can play a role in HIV-1 vaccines

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natural form. Future studies should also investigate whether mRNA vaccines can generate HLA-E CD8+ T-cell responses by targeting dendritic cells, as these antigen-presenting cells have increased expression of HLA-E. In summary, mRNA vaccines can quickly test new strategies and have the potential to generate a multifaceted, complex immune response that will ultimately be required to protect against HIV-1 infection.

Future Advances in mRNA Vaccine Technology

In addition to HIV-1, mRNA vaccine technology is being investigated for the prevention of other infections, with ongoing clinical trials examining mRNA vaccines targeting respiratory syncytial virus, influenza viruses, Zika virus, rabies virus, Ebola virus, and malaria.[4] Recent advances in mRNA vaccine technology may prove to be beneficial for preventing these infections as well.

mRNA vaccines can quickly test new strategies and have the potential to generate a multifaceted, complex immune response that will ultimately be re-quired to protect against HIV-1 infection

One of these advances is self-amplifying mRNA. This strategy involves including a viral replicase gene in the vaccine open reading frame in addition to a designed antigen target.[67] In a study performed in mice, this strategy led to a 10-fold increase in protein expression and increased the duration of antigen detection from 2 days to 10 days.[68] Using this strategy not only increases immunogenicity by prolonging antigen presentation but also decreases the amount of mRNA needed. This would decrease PRR recognition and the innate immune response, leading to stronger adaptive immune responses and ultimately improved antibody responses, such as generation of bNAbs by an HIV-1 vaccine. This strategy may also induce longer-lasting antibodies, which has been a particular problem with the existing mRNA platforms.[69]

Other ongoing research is focused on optimizing mRNA vaccines to target specific tissues and cells. Achieving this would allow researchers to target immune response toward the area where infection is most likely to occur. For SARS-CoV-2 and influenza viruses, vaccine immune responses in the upper respiratory system are crucial, whereas genital and rectal mucosal immune responses are much more important in combating HIV-1. Another strategy involves using mRNA to target specific immune cells. As mentioned previously, specific lipid nanoparticle formulations have been found to stimulate stronger Tfh-type responses.[63] Other groups are investigating how to generate a strong dendritic cell response, which can lead to improved antigen presentation and stronger overall immune responses.

Several limitations to mRNA vaccine technology merit discussion. One is temperature storage requirements, which currently are temperatures of –20 °C or colder. This will be a major obstacle for HIV-1 vaccines, as much of the developing world where HIV-1 is most prevalent does not have the infrastructure required to store vaccines at this temperature. From an immunologic standpoint, there is also the limitation that antibody responses generated from mRNA vaccines alone appear to be less durable compared with vaccination in the context of prior infection.[70] Although continuing to boost vaccine responses is possible, this may not be a cost-effective method when trying to vaccinate a large number of individuals. It is also important to note that the mRNA technology is still relatively new and only COVID-19 vaccines are FDA approved using this platform. Time will tell whether the mRNA platform can be consistently used to develop vaccines targeting other pathogens.

From an immunologic standpoint, antibody responses generated from mRNA vaccines alone appear to be less durable compared with vaccination in the context of prior infection

Conclusion

The use of mRNA vaccine technology to create safe and effective vaccines quickly during the COVID-19 pandemic has been one of the most remarkable achievements of medical research of our generation. Meanwhile, HIV-1 vaccine efforts fail to elicit effective protection. However,

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the HIV-1 vaccine field now has a clear goal to create a vaccine that induces bNAbs, and there are several new strategies that show promise in this regard. It is likely that a multifaceted immune response will be needed, generating potent HIV-specific bNAbs, an optimal CD4+ T-cell response, and a strong CD8+ T-cell response. mRNA vaccine technology is a powerful vaccine platform to test these new strategies, with the potential to benefit ongoing HIV-1 vaccine research efforts.

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Reviewer 1 reported consulting or advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and Gilead Sciences, Inc. (Updated March 6, 2024) Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies. (Updated March 6, 2024)

All relevant financial relationships with ineligible companies have been mitigated.

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Invited Review

Long-Term Effects of COVID-19: The Stories of 2 Physicians Who Became Patients

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Approximately 10% of patients who survive COVID-19 will proceed to have lasting, often debilitating effects, known as "long COVID." These symptoms can take various forms, most commonly including postexertional malaise, fatigue, brain fog, dizziness, gastrointestinal symptoms, heart palpitations, diminished sexual desire or capacity, loss of smell or taste, thirst, chronic cough, chest pain, and abnormal movements. Here, 2 physician-patients present their own experiences with long COVID and share their perspectives on the experience. One key insight is that patients who are not familiar with long COVID may not attribute ongoing symptoms to their illness. Diagnosis requires an astute, compassionate physician who understands long COVID and can appropriately situate the symptoms within the evolving understanding of the condition, leading the patient toward recovery.

Keywords: long COVID, PASC, SARS-CoV-2, patient narrative

Introduction

Although vaccination and treatment have significantly reduced the mortality associated with COVID-19, many people who become infected with SARS-CoV-2 continue to experience persistent physical or mental symptoms, commonly referred to as "long COVID." According to the Centers for Disease Control and Prevention, long COVID is defined as "signs, symptoms, and conditions that continue or develop after acute COVID-19 infection."[1] These symptoms can begin during or immediately after the acute phase of COVID-19 and last weeks to years. The symptoms vary from person to person, ranging from mild to debilitating.

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An estimated 200 symptoms have been associated with long COVID, of which the 12 most common are postexertional malaise, fatigue, brain fog, dizziness, gastrointestinal symptoms, heart palpitations, diminished sexual desire or capacity, loss of smell or taste, thirst, chronic cough, chest pain, and abnormal movements.[2] Many people with these symptoms of long COVID remain undiagnosed and untreated, which can substantially affect their lives and even jeopardize their livelihoods. Individuals most likely to be affected are those with comorbid conditions, those who are unvaccinated, and those who experienced severe disease requiring hospitalization or intensive care.[1] Thus, members of vulnerable populations that were disproportionately affected by COVID-19 are more likely to develop long COVID.

Responses to the US Census Bureau Household Pulse Survey from June 2023 indicate that approximately 10% of adults in the US who were infected with COVID—or approximately 10 million Americans—have experienced long COVID.[2] Another study with a more global patient population showed the prevalence of long COVID among those ever infected with COVID to be between 10% and 35%.[3] Furthermore, long COVID has been shown to affect those who tested positive for COVID-19 and those who tested negative but experienced persistent symptoms after an acute illness consistent with COVID-19.[1] This finding could point to an even larger number of people affected by long COVID than reported in these studies. Although research is ongoing, the impacts are substantial and need to be addressed to help these patients understand and manage their symptoms.

Our intention in this article is to generate more awareness about long COVID and encourage patients to reflect on their symptoms and seek medical help as needed. Because the symptoms can vary and may not be recognized as being related to long COVID, sharing personal stories about long COVID may help others who are affected. To accomplish this goal, we present the personal stories of 2 patients, both physicians, who experienced long COVID but identified it at very different stages, leading to differing approaches to dealing with their symptoms.

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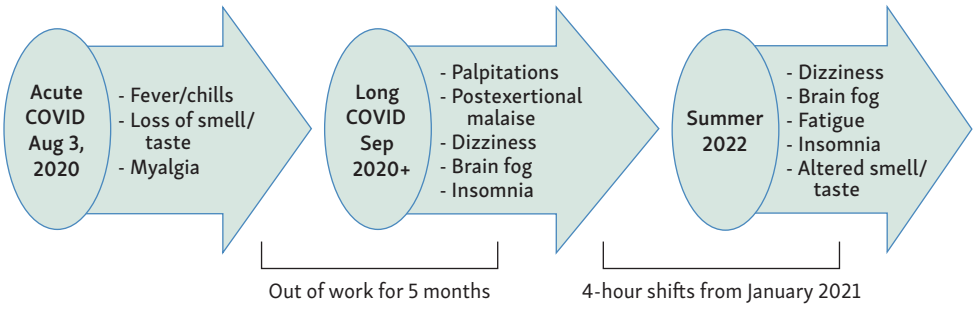

Figure 1. Patient 1 Disease Timeline.

Patient 1 is an emergency medicine physician who immediately recognized his symptoms as being related to COVID-19 and sought medical attention early in the disease course at a time when long COVID was less well understood. Patient 2 is an emergency medicine resident physician who experienced his symptoms without recognizing their etiology and identified them as long COVID only after hearing the story of patient 1. Although these are only 2 stories of long COVID, they show that the effects of long COVID are real, even if the condition is still not fully understood. Identifying the symptoms as being related to COVID-19 is an important first step to helping and offering validation to individuals with long COVID.

Patient 1

On August 2, 2020, I worked a normal evening shift in the emergency department. The next day, I awoke with a headache that began what has become a 3-year ongoing journey first with acute COVID-19 and then with long COVID (Figure 1).

The first week, my symptoms were mild. I had low-grade fevers, headaches, myalgia, and chills, with most of these symptoms being worse in the evenings. Altered senses of smell and taste began on day 2, an experience that was at first more interesting than worrisome. My children made me a tasting plate and delighted when the only items I could taste were the most artificially flavored candies. I was fortunate to be able to quarantine in our basement, protecting my family from infection during the time before vaccines. I worked a bit, watched movies, did puzzles, and waited.

The waiting droned on. Fevers continued daily for 40 days. Headaches and altered taste and smell continued unchanged and my other symptoms began to evolve. Myalgia and chills gave way to palpitations and insom-nia. I had trouble falling asleep and then would wake during the night with a pounding heart, unable to fall back to sleep for more than an hour on many nights. As I walked in the neighborhood, I noticed that if I went more than half a mile, or if I bounded up stairs too quickly, I would become completely exhausted, unable to rise from the couch for hours. This fatigue would usually have a delayed onset. I often felt that I had the energy to do anything, but I would pay for it later with what is best described as a completely drained battery.

As weeks turned into months, and as attention turned to long COVID in the medical literature and the media, I began to understand other symptoms I had been experiencing. Although I never had the word-finding difficulties and memory problems that many with brain fog describe, I did notice clouded cognition, especially after either physical or mental exertion. A long walk could bring it on as easily as a long video conference call. The brain fog went hand in hand with the fatigue.

Emotionally, this situation took a heavy toll on my family and me. I tried to stay positive, taking comfort in the perspective I had gained in the emergency department during the preceding months, seeing how much worse things could have been. I focused my att-ention on the present, trying to stay in a position of mindfulness while my mind tended to wander to what the future might hold. However, the uncertainty about how our lives could be permanently altered by this illness and whether I would be able to return to work weighed on us.

As weeks turned into months, and as attention turned to long COVID in the medical literature and the media, I began to understand other symptoms I had been experiencing

Throughout these months, I underwent many medical examinations and tests. My first COVID polymerase chain reaction test (on day 0) was negative, as was a subsequent test (on day 18). Although COVID-19 remained the most likely diagnosis based on exposure and symptom profile, my primary care physician tested broadly for alternative illnesses and referred me to our

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institution's respiratory clinic for further testing. All the results were normal. Even the antibody tests were frustratingly negative, and we would not learn until later that this situation is all too common in individuals with long COVID, perhaps offering a clue to the etiology of the condition. The only abnormality that stood out was new hypertension. I was a fit 40-year-old man when I became sick, and 3 weeks into COVID-19 my blood pressure was consistently averaging 180/100 mm Hg or higher.

My primary care physician referred me to a cardiologist with expertise in dysautonomia, and that was when I finally started to see some improvement. The cardiologist identified dysautonomia and prescribed a calcium-channel blocker and antihistamines. The palpitations subsided, and my fatigue improved substantially. The headaches improved too. For the first time, I had hope of returning to work and to my life. That would take time, however. For the time being, I welcomed the improvement and continued to adapt both at home and in my nonclinical work to accommodate my symptoms.

Over these 3 years, I have seen many specialists and engaged in continuous efforts to evaluate different medications, therapies, and lifestyle changes to improve my health. Much of this response was driven by the dedicated study and compassion of my physicians. Some of it was driven by ideas mentioned on social media or in patient support groups. I began to finally understand the value of these forums for patients like me who were not finding complete symptom relief despite the best medical efforts.

Having long COVID had substantial consequences at home and at work. Personally, I was not able to be the dedicated husband and father my family had depended on. I could not play actively with my children or be relied on to handle the day-to-day driving related to their activities. At work, I regretted the added strain my absence put on an already taxed faculty. I was out of work for 5 months and then able to work only part-time until just this spring. Initially, I was able to work only 4-hour shifts and then very gradually advanced up to 8 hours, with a setback when I was reinfected at a medical conference in 2021. I was able to do many of my nonclinical activities remotely, teaching and meeting with residents, but I had to adapt my efforts to my symptoms. I could not participate in residency application review or interviews for the first couple of years because of fatigue and brain fog.

Over these 3 years, I have seen many specialists and engaged in continuous efforts to evaluate different medications, therapies, and lifestyle changes to improve my health

I continue to improve very slowly. Although I believe that I will have lifelong lasting effects from COVID-19, I also retain hope that my symptoms will continue improving to a point at which they no longer affect my daily activities.

I was able to work only 4-hour shifts and then very gradually advanced up to 8 hours, with a setback when I was reinfected at a medical conference in 2021

Patient 2

It was not until the end of my first year as an emergency medicine resident physician on June 13, 2023, that I took stock of symptoms that started after I had COVID-19. I first contracted COVID-19 at the end of December 2021 following a family holiday gathering, our first such gathering since the beginning of the pandemic. We were all fully vaccinated and had decided that it was safe enough to have a family vacation. This was at the peak of the epidemic wave of the Omicron variant. At the end of the weeklong vacation, it was clear that most of us had been exposed to the virus. After returning home on January 1, 2022, I tested positive for COVID-19. My symptoms included a severe sore throat, cough, fever, myalgia, and allodynia. Thankfully, I never lost my sense of taste, which some of my family members had reported. I felt moderately ill. I quarantined from my wife and managed my symptoms supportively with fluids and an occasional antipyretic. I never developed any severe symptoms that would warrant going to the hospital. After about 10 days, my symptoms had improved, and I thought that I had survived COVID-19. As a healthy man in his mid-30s who was fully vaccinated, I did not expect anything different; however, my journey had just begun (Figure 2).

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Having recovered from the acute phase of COVID-19, I was finally able to end my quarantine. Shortly thereafter, I started noticing new symptoms, which included post-exertional fatigue, brain fog, word-finding difficulties, and memory problems. I would become overly fatigued during the day if I did not get enough sleep and easily became short of breath while walking up the stairs to our third-floor apartment. Still, I was not concerned. I thought that these were transient symptoms that would soon resolve.

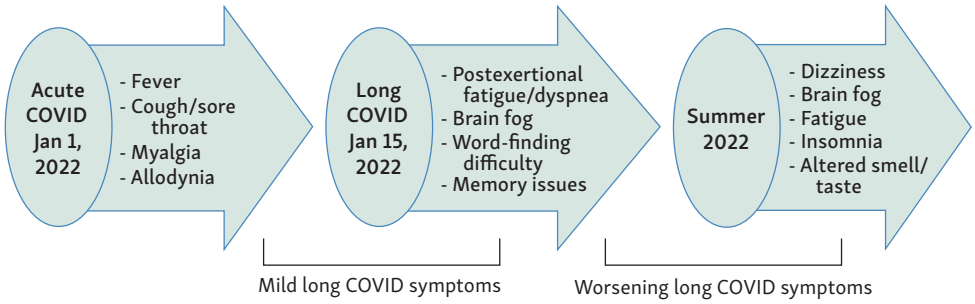

Figure 2. Patient 2 Disease Timeline.

Professionally, I was in my fourth year as a medical student with no clinical obligations, a lot of free time, and minimal cognitive demands. I spent a good amount of time watching my favorite shows and getting enough rest, which masked my cognitive symptoms. Every now and then, I would forget the names of my colleagues and even some close friends. I thought that I might be watching too many streaming shows. The next few months were filled with important life events, including finding out where I would be doing my emergency medicine residency, graduation, and ultimately starting my residency training.

> ***I found myself having difficulty concentrating and felt like I could not think clearly, especially toward the end of my shifts***

It was now July 2022, six months after I was first diagnosed with COVID-19. I had moved to a new city and started my new job as an emergency medicine resident physician. The increased cognitive demands that my new job entailed put a spotlight on my ongoing symptoms. I could no longer ignore them.

I found myself having difficulty concentrating and felt like I could not think clearly, especially toward the end of my shifts. The brain fog was all too real now. I was also having more difficulty remembering seemingly simple things, including the names of my colleagues and friends. Additionally, whenever I did not get enough sleep, I was overly fatigued and rendered almost dysfunctional the following day. I was still having postexertional dyspnea, but it had improved.

The word-finding difficulties were the most debilitating and bothersome to me. I often found myself frozen in time, unable to verbalize words that were familiar to me, while delivering patient reports or presentations to my supervisors or in casual conversations. I had the words in my mind and could visualize them, but I simply could not verbalize them. I was unable to piece together what was happening to me. I thought that maybe this was what being in my mid-30s entailed: I had begun an early neurocognitive decline, and that was that. However, I was determined to not let these symptoms beat me. I decided to do something about the situation.

I downloaded word puzzles on my phone and enlisted my wife as my partner in my quest to either reverse or slow my brain fog and memory problems. I had a nightly routine of completing word puzzles, which I thought would help improve my cognitive function. Although I noticed some improvement over time, there was no complete resolution or return to my baseline. My life had changed, and I could not explain why. This was my "new normal."

I had not reflected on the fact that all of these symptoms were directly correlated with my COVID-19 illness. My physical symptoms including postexertional dyspnea had gradually improved but not resolved, making them even less identifiable as post-COVID effects. The mental symptoms had lingered and were now significantly affecting my life. Although they were not disabling enough to affect my clinical work, I found that I had to do more, read more, and work harder to retain the same information as previously.

It was not until a year later, when the preceding story of long COVID was shared by my program director, that it dawned on me that I too had been suffering from long COVID. Whereas his symptoms were obvious, making them easily identifiable and attributable to COVID-19, mine were more subtle at first and amplified only later, when I started engaging in more cognitively demanding tasks. After my program director shared his story, he

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Table. Medications and Therapies That Patient 1 Tried During His Long COVID Illness

Therapy	Intended symptom target
Atrioventricular nodal blockers (diltiazem, nadolol, clonidine, metoprolol)	Palpitations
Stimulants/antidepressants (bupropion, fluoxetine, amantadine, atomoxetine)	Brain fog, malaise
Antihistamines (H1 and H2 blockers)	Brain fog, malaise
Anticoagulants (apixaban, clopidogrel, aspirin)	Brain fog, malaise
Sleeping pills (eszopiclone)	Insomnia
Low-dose naltrexone	Brain fog, malaise
Supplements (B complex, C, D, magnesium, zinc, thiamine, quercetin, coenzyme Q10, nattokinase)	Malaise and overall health
Levine protocol postural orthostatic tachycardia syndrome exercise regimen	Dysautonomia
Compression stockings (20-30 mm Hg)	Dysautonomia
Sleep hygiene	Insomnia
Acupuncture	Malaise, brain fog
Hyperbaric oxygen therapy	Brain fog
Diet change	Overall health
Saphenous vein ablation	Dysautonomia
Stellate ganglion block	Dysgeusia, dysautonomia
Essential oil olfactory training	Dysgeusia

helped me reflect on my own experience and start seeking medical help to deal with the residual symptoms of my COVID-19 illness.

My symptoms have improved substantially over the prior year, but 18 months after I was first diagnosed with COVID-19, I still have intermittent brain fog, some word-finding difficulties, and memory problems. These issues are not debilitating enough to affect my daily life, but they are enough to make me realize that my body and brain changed after my infection with SARS-CoV-2.

Since coming to terms with long COVID, I have had many conversations with family members and friends who have reported similar symptoms that followed their acute COVID-19 illness, persisting for months and even years. They too have realized that they have been casualties of COVID-19 and have been suffering with long COVID well after their acute infection.

Discussion

These 2 stories of physician-patients with long COVID can teach us many lessons about the realities of this condition and its impacts on people's lives. Although there is some overlap of their symptoms, there are also some notable differences, especially in the degree of severity of the illness and the effects that it had on their lives. The 2 patients experienced 5 of the 12 most common symptoms reported by long COVID patients: postexertional malaise, fatigue, brain fog, heart palpitations, and loss of taste. Importantly, patient 1 never tested positive for COVID-19, whereas patient 2 had a positive test result. This experience is consistent with the data surrounding long COVID, which show that some patients may have negative test results.[1] It is important to keep this fact in mind when addressing patients who have symptoms consistent with long COVID.

The differences in the 2 patients' courses of disease and how they dealt with their symptoms are also informative. On one hand, patient 1 experienced symptoms immediately after his acute illness, which continued to progress. His symptoms were debilitating, rendering him incapable of returning to work. Thankfully, his health care practitioners compassionately helped him navigate his symptoms at a time when even less was known about long COVID than today. His laboratory test results were all normal, making it harder to make a diagnosis. The Table shows the many medications he tried in his quest for recovery. For patient 2, the symptoms also presented shortly after his acute illness, but they were initially mild, becoming more pronounced months later when he was required to exert himself mentally. He did not immediately recognize the symptoms as being related to COVID, and only later, after listening to the story of patient 1, did he identify them as representing long COVID. Although identifying and dealing with long COVID was very different for these 2 patients, the impacts on their lives were significant.

The same is likely true for the millions of other people affected by long COVID. Although some of these individuals may quickly identify their symptoms and even seek treatment for them, many more are likely going undiagnosed and untreated. For those who seek medical help, the results of laboratory tests and imaging modalities will often be negative,[1] which may complicate

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the management of their illness by physicians who may be unfamiliar with long COVID and its effects.

Given the evolving but incomplete understanding of long COVID, it is important to bring awareness to this emerging disease and begin to make changes in how we diagnose and treat patients suffering from it. As demonstrated in these 2 stories, many people with long COVID may not be actively seeking answers about what is happening to their bodies but may be suffering in silence. Others may be engaging with the health care system without finding relief. Both behaviors can lead to a worse quality of life. These effects may be mitigated with proper understanding and support by medical professionals, who can help set these patients on the road to recovery and, more importantly, offer validation and support. It is therefore important for clinicians to familiarize themselves with long COVID and keep it among their potential differential diagnoses for patients who present with symptoms that cannot be easily explained. The support that these patients receive from their health care providers can be crucial in helping them begin to navigate the effects of COVID-19 and cope with the impact the disease continues to have on their lives.

This article was based on a presentation by Jeffrey N. Siegelman, MD, at the IAS-USA State-of-the-Art Update on Long COVID and HIV: Pathogenesis, Management, Clinical Trial Updates, and a Patient Perspective, on June 22, 2023.

The IAS–USA will identify and resolve ahead of time any possible conflicts of interest that may influence continuing medical education (CME) activities with regard to exposition or conclusion. All financial relationships with ineligible companies for the authors and reviewers are listed below.

Financial relationships with ineligible companies within the past 24 months: Dr Siegelman reported no relevant financial relationships with ineligible companies. (Updated February 29, 2024) Dr Mwangi reported no relevant financial relationships with ineligible companies. (Updated February 29, 2024)

Reviewer 1 reported consulting or advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and Gilead Sciences, Inc. (Updated March 6, 2024) Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies. (Updated March 6, 2024)

All relevant financial relationships with ineligible companies have been mitigated.

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Case Report

The Challenge of Adherence to a Complex Antiretroviral Therapy Regimen in an Individual With Multidrug-Resistant HIV

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Abstract: *Limited therapeutic options are available for patients with multidrug-resistant HIV. This report describes a 38-year-old female who was perinatally infected with HIV-1 and treated with 14 different antiretroviral regimens over 27 years, gradually leading to 4-class drug resistance. Despite various attempts to obtain sustained viral suppression, including the off-label administration of intravenous foscarnet and enfuvirtide, and thorough follow-up with 16 viral genotyping/phenotyping from 1999 to 2021, viral control was not maintained. Recently, the introduction of a regimen with fostemsavir and lenacapavir resulted in long-term viral suppression.*

Keywords: HIV, AIDS, multidrug resistance, integrase strand transfer inhibitor, resistance, foscarnet, fostemsavir, lenacapavir

Introduction

The number of people who are living with HIV and receiving antiretroviral therapy (ART) is increasing worldwide. Incomplete viral suppression because of low adherence or suboptimal ART leads to the emergence of HIV resistance-associated mutations. The most affected classes are nucleoside reverse transcriptase inhibitors (nRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs).[1-5] Epidemiologic studies in high-income countries, including Belgium, reported a prevalence of 2.4% to 10% in baseline resistance to at least 1 drug in each of the nRTI, NNRTI, and protease inhibitor (PI) classes.[4,5] Resistance-associated mutations to the first-generation integrase strand transfer inhibitors (InSTIs), raltegravir (RAL) and elvitegravir (EVG), were reported in fewer than 1% of drug-naive patients with HIV in Belgium.[5] Acquired triple-class drug resistance seems to be more common in patients who acquired HIV perinatally, especially if treatment adherence issues are observed. Moreover, delay before starting ART is often longer in patients with perinatal HIV.[4]

Fostemsavir (FTR) is a first-in-class attachment inhibitor that binds to glycoprotein 120 in the viral envelope. Preliminary results of a phase III study showed complete viral suppression at week 48 in 54% of the individuals with multidrug-resistant HIV and randomly assigned to FTR combined with optimized background therapy.[6] Lenacapavir (LEN) is a first-in-class inhibitor of the HIV-1 capsid, and its in vitro and in vivo activity is maintained against viruses harboring mutations responsible for resistance to nRTIs, NNRTIs, PIs, and InSTIs.[7,8]

Few reports describe the treatment for patients with multidrug-resistant HIV.[9-11] Rescue strategies include anti-CD4 monoclonal antibody therapy and immunoglobulin administration combined with ART. Other studies evaluated foscarnet (FNT) administration for rescue therapy.[12,13] Nevertheless, clinical data on rescue strategies in individuals with multidrug-resistant HIV are few. This article describes a patient with extremely drug-resistant HIV-1 with complete resistance to the 4 main ART classes, including second-generation InSTIs. The

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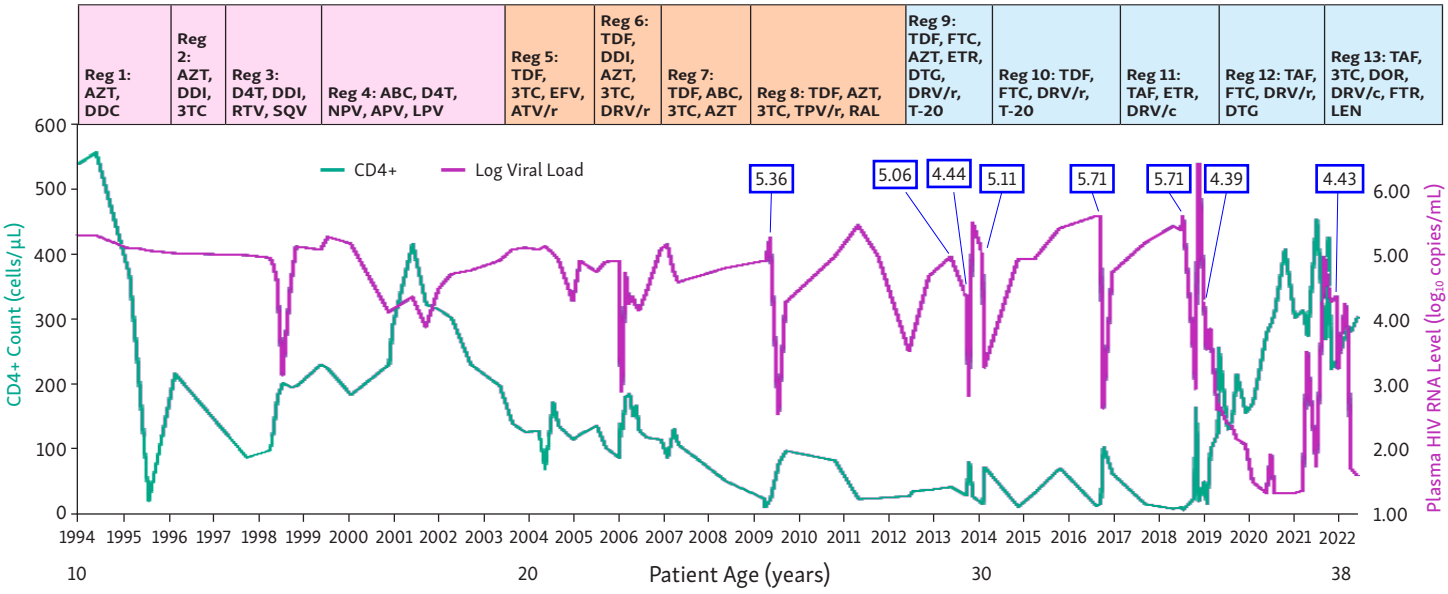

Figure. Evolution of the Antiviral Regimens, Respective CD4+ Counts, and HIV-1 Plasma HIV RNA Levels. x-axis, timeline; y-axis, CD4+ count (cells/µL) in green and plasma HIV RNA level (log_{10} copies/mL) in purple. Values in dark blue boxes represent viral plasma HIV RNA level before hospitalization. The boxes at the top of the graph denote the sequential antiviral regimens, with the color of the boxes related to the degree of HIV resistance; pink boxes indicate HIV resistance to 1 drug within 2 antiviral classes, orange boxes indicate resistance to 3 classes, and light blue boxes indicate resistance to 4 classes.

Abbreviations: /c, boosted with cobicistat; /r, boosted with ritonavir; 3TC, lamivudine; ABC, abacavir; APV, amprenavir; ATV, atazanavir; AZT, zidovudine; D4T, stavudine; DDI, didanosine; DDC, zalcitabine; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; FTC, emtricitabine; FTR, fostemsavir; LEN, lenacapavir; LPV, lopinavir; NPV, nevirapine; Reg, regimen; RAL, raltegravir; RTV, ritonavir; SQV, saquinavir; T-20, enfuvirtide; TAF, tenofovir alafenamide; TDF, tenofovir; TPV, tipranavir.

resistance-associated mutations were investigated by serial genotyping drug resistance tests. Off-label therapies that were implemented for this treatment-experienced patient are described.

Case Report

This patient is a woman who was born in the Democratic Republic of Congo in 1984 and arrived in Belgium in 1993 when 9 years old. Her mother died from AIDS before the patient arrived in Belgium. The patient was diagnosed in February 1993 with HIV-1 and active hepatitis B virus infections. Over the course of the patient's treatment, hepatitis B was inconsistently controlled depending on the compliance with the various treatments covering both HIV and hepatitis B. The Figure summarizes the history of the patient's antiviral regimens and the evolution of her CD4+ T-cell count and plasma HIV RNA level load over time. In 1995, the CD4+ T-cell count was 17/µL and the plasma HIV RNA level was 157,000 copies/mL. The patient was enrolled in a clinical trial and treatment was started with zidovudine 200 mg 3 times daily combined with placebo. After 4 months, she was switched to the active study medication, zalcitabine 0.75 mg 3 times daily and zidovudine (Figure, ART regimen 1). Her first phenotypic drug resistance test, requested because of suboptimal viral suppression, was performed in 1999 with an HIV phenotype antivirogram (Virco NV). The test results triggered an aggressive ART regimen switch to abacavir 300 mg twice daily, stavudine 300 mg twice daily, nevirapine 200 mg twice daily, amprenavir 600 mg twice daily, and lopinavir 200 mg twice daily (Figure, ART regimen 4). However, suboptimal viral control persisted and various attempts were made to achieve viral suppression. Subsequent genotypic drug resistance tests were performed using the Trugene HIV-1 Genotyping Kit (Siemens) or in-house-developed Sanger sequencing techniques on an Applied Biosystems, Inc (ABI) platform (all of which are compliant with International Organization for Standardization 15189 standards) followed by resistance predictions using the Stanford HIV Drug Resistance Database version available at the time of sampling.[14] Resistance-related mutations were investigated in the PR (PI), RT (nRTIs, NNRTIs), INT (InSTIs), and gp120 genes (fostemsavir and maraviroc). Genotypic tropism was predicted using the Geno2Pheno website.[15,16] Therapy changes and dosing were mainly based on the drug susceptibility results available at the time (Table 1). In 2009, the patient was hospitalized with *Pneumocystis jirovecii* pneumonia and diagnosed with

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Table 1. Overview of the Resistance Profiles Available to the Clinicians at Sample Date

Sample date	Oct 11, 1999	Jul 10, 2003	Oct 11, 2004	Jan 23, 2006	Jul 31, 2006	May 10, 2007	Nov 2, 2009	Jun 10, 2011	Nov 17, 2011	Dec 19, 2011	Aug 28, 2012	Dec 20, 2012	Jan 7, 2013	Oct 3, 2013	Aug 31, 2018	Nov 22, 2021	Cumulative
Phenotype (2), virtual phenotype (VP). or genotype (G)	P	G	G	VP	VP	VP	G	G	G	P	G	P	G	P	G	G	G
Treatment at time of resistance profile	D4T, DDI, RTV, SQV	ABC, D4T, NPV, APV, LPV	TDF, 3TC, EFV, ATV/r	TDF, DDI, AZT, 3TC, DRV/r	TDF, DDI, AZT, 3TC, DRV/r	TDF, ABC, 3TC, AZT	TDF, AZT, 3TC, TPV/r, RAL	TDF, AZT, 3TC, TPV/r, RAL	TDF, AZT, 3TC, TPV/r, RAL	TDF, AZT, 3TC, TPV/r, RAL	TDF, FTC, AZT, ETR, DRV/r, DTG, T-20	TDF, FTC, AZT, ETR, DRV/r, DTG, T-20	TDF, FTC, AZT, ETR, DRV/r, DTG, T-20	TDF, FTC, AZT, ETR, DRV/r, DTG, T-20	TAF, ETR, DRV/c	TAF, 3TC, DOR, DRV/c, FTR, LEN	
nRTI																	
Lamivudine (3TC)	ILL	S	S	IR	IR	IR	R	R	R	R	R	R	ILL	R	R	S	R
Abacavir (ABC)	S	R	ILL	R	IR	ILL	R	R	R	R	R	R	R	R	R	R	R
Zidovudine (AZT)	R	R	ILL	ILL	ILL	ILL	R	R	R	R	R	R	R	R	R	R	R
Stavudine (D4T)	S	R	ILL	ILL	ILL	ILL	R	R	R	R	R	R	R	R	R	R	R
Didanosine (DDI)	S	R	R	ILL	ILL	IR	R	R	R	R	R	R	R	R	R	R	R
Emtricitabine (FTC)	–	–	–	R	R	R	R	R	R	R	R	R	ILL	R	R	S	R
Tenofovir (TDF)	–	R	R	IR	IR	ILL	ILL	ILL	ILL	S	R	R	R	R	R	IR	R
NNRTI																	
Doravirine (DOR)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	IR	R
Efavirenz (EFV)	S	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Etravirine (ETR)	-	-	-	-	-	-	R	R	R	S	R	SP	R	SP	R	R	R
Nevirapine (NVP)	S	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Rilpivirine (RPV)	–	–	–	–	–	–	–	–	R	–	R	–	R	–	R	R	R
PI																	
Atazanavir (ATV/r)	–	–	ILL	R	R	IR	R	R	R	R	R	R	R	R	R	R	R
Darunavir (DRV/r)	–	–	–	–	ILL	ILL	IR	IR	IR	SP	IR	SP	IR	SP	R	R	R
Fosamprenavir (FPV/r)	–	–	–	R	R	IR	R	R	R	R	R	R	R	R	R	R	R
Indinavir (IDV/r)	S	R	R	IR	S	ILL	R	R	R	S	R	R	R	S	R	R	R
Lopinavir (LPV/r)	-	R	R	IR	ILL	ILL	R	R	R	SP	R	SP	R	R	R	R	R
Nelfinavir (NFV)	R	R	R	IR	IR	IR	R	R	R	R	R	R	R	R	R	R	R
Ritonavir (/r)	R	R	R	R	–	–	–	–	–	–	–	–	–	–	–	–	–
Saquinavir (SQV/r)	ILL	R	R	IR	ILL	ILL	R	R	R	R	R	R	R	R	R	R	R
Tipranavir (TPV/r)	–	–	–	R	ILL	ILL	ILL	ILL	ILL	SP	IR	SP	IR	SP	R	R	R

Continued on next page

depression and personality disorders. Based on genotypic analysis, treatment was initiated with tenofovir 245 mg daily, lamivudine 150 mg twice daily, zidovudine 300 mg twice daily, tipranavir 500 mg twice daily, ritonavir 200 mg twice daily, and raltegravir 400 mg twice daily (Figure, ART regimen 8), and resulted in a plasma HIV RNA level reduction of 3.3 $\log_{10}$ copies/mL followed by an increase of 1.78 $\log_{10}$ copies/mL 2 months later.

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Table 1. Overview of the Resistance Profiles Available to the Clinicians at Sample Date *(continued from previous page)*

Sample date	Oct 11, 1999	July 10, 2003	Oct 11, 2004	Jan 23, 2006	Jul 31, 2006	May 10, 2007	Nov 2, 2009	Jun 10, 2011	Nov 17, 2011	Dec 19, 2011	Aug 28, 2012	Dec 20, 2012	Jan 7, 2013	Oct 3, 2013	Aug 31, 2018	Nov 22, 2021	Cumulative
InSTI																	
Bictegravir (BIC)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	S	R	R
Cabotegravir (CAB)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	R	R
Dolutegravir (DTG)	–	–	–	–	–	–	–	–	–	S	–	SP	R	R	S	R	R
Elvitegravir (EVG)	–	–	–	–	–	–	ILL	ILL	ILL	–	R	–	R	–	SP	R	R
Raltegravir (RAL)	–	–	–	–	–	–	ILL	ILL	R	R	R	SP	R	R	SP	R	R
Fusion and attachment inhibitors																	
Enfuvirtide (T-20)	–	–	–	–	–	–	–	–	–	S	–	–	–	S	–	–	–
Maraviroc (MVC)	–	–	–	–	–	–	–	CXCR4 use	–	Dual/ mixed CCR5 use predo- mi- nant	–	Dual/ mixed CCR5 use limi- ted	–	Dual/ mixed CCR5 use limi- ted	–	–	–

The cumulative result is based on all mutations detected over time in the genotypic drug resistance tests and interpreted by the current Stanford algorithm, version 9.1. Antiretroviral regimens over time are sequentially expressed and numbered in the upper part of the figure. Antiretroviral medicine names and their abbreviations are presented in column 1. Abbreviations: /c, boosted with cobicistat; /r, boosted with ritonavir; InSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; ILL, low-level resistance; IR, intermediate resistance; R, high-level resistance; S, susceptible; SP, potential low-level resistance; -, result not available.

The nonpolymorphic mutation in XX (E138K) was already present in 2008. Raltegravir was started in 2009 and the associated polymorphic INT mutation E157Q appeared soon after. According to the Stanford HIV database, the presence of mutations E138K and E157Q should not reduce susceptibility to an InSTI but its scoring system does report low-level resistance to raltegravir and elvitegravir. After 2 years of ART that included raltegravir, mutation Y143R, which is associated with high-level resistance to raltegravir, emerged.

As the therapeutic options were limited, a strategy was designed including intravenous (IV) foscarnet 90 mg/kg/dose twice daily and IV enfuvirtide 90 mg twice daily followed by optimized ART with high-dose dolutegravir and subcutaneous enfuvirtide (Figure, ART regimen 9). Phenotypic susceptibility tests for enfuvirtide were performed in 2011 and 2013, showing conserved drug sensitivity (fold changes, 0.67 and 1.32, respectively). Therapy intensification with IV foscarnet and IV enfuvirtide was repeated in 2014, 2016, and 2018 to attempt viral suppression. However, sustained virologic control was not achieved. Between the periods of regimen intensification with IV antiretrovirals, plasma HIV RNA level increased consistently up to 5.71 $\log_{10}$ copies/mL with CD4+ T cells gradually dropping from 70/µL to 3/µL. In 2019, the patient presented with a wasting syndrome (body mass index, 14 kg/m^2), memory loss, and increasing depression. A progressive multifocal leukoencephalopathy was diagnosed as well as a generalized infection with *Mycobacterium avium* complex, for which adequate treatment was initiated. After multidisciplinary discussion and patient agreement, a gastrostomy was placed because the patient was intolerant to oral antiviral therapy. Thereafter, a new regimen was started with IV foscarnet and enfuvirtide with optimized ART (Figure, ART regimen 12). Acute renal failure and severe myocarditis prompted the discontinuation of foscarnet and the patient was admitted to the intensive care unit until clinical resolution. Three months after the therapy intensification, the patient had gained 12 kg with partial CD4+ T-cell count recovery and had an undetectable plasma HIV RNA level for 18 months. In 2021, the patient developed virologic failure again and a sixth regimen intensification with the same IV molecules was proposed. Mutations S375H/I/M/N/T, M426L/P, M434I/K, and M475I of the envelope glycoprotein 120 HIV-1 gene

related to fostemsavir resistance[16] were not detected in samples from June and November 2021. In January 2021, doravirine 100 mg daily and fostemsavir 600 mg twice daily were added to the regimen. A few months later, the ART regimen was reinforced with oral initiation and thereafter subcutaneous lenacapavir 300 mg administered every 6 months (Figure, ART regimen 13). Viral suppression was achieved in May 2022 with partial immune reconstitution (CD4+ T-cell count, 287/μL), which continued to the date of this report on November 14, 2023 (viral load, <20 copies/mL; CD4+ T-cell count, 364/μL).

Discussion

This case report describes a patient who developed highly drug-resistant HIV with a well-documented evolution of resistance with serial genotyping and phenotyping drug resistance tests.

The patient was perinatally HIV-1 infected and met the definition of AIDS when ART was initiated. When the first drug susceptibility tests were available in 1999, limited resistance-associated mutations were observed. However, after years of suboptimal viral suppression due to severe treatment-adherence issues, a virus almost completely resistant to all drugs in the nRTI, NNRTI, and PI classes was isolated in 2004. From 2004 to 2008, due to the lack of fully active ARV options, the patient was on suboptimal ART. The susceptibility test performed in 2013 demonstrated complete resistance to raltegravir (fold change more than maximal, >100) and dolutegravir (fold change, 21). Several attempts to control HIV replication with innovative strategies were performed, including an induction phase with foscarnet, which is generally used to treat the *Herpesviridae* family of infections. Foscarnet inhibits viral polymerases and has anecdotally been used in regimens for multidrug-resistant HIV.[12,13] Nephrotoxicity is a common adverse effect and cardiotoxicity a rare adverse effect of this drug.[17] It is likely that the reversible myocarditis was linked to foscarnet, because it was acquired in the hospital 1 week after treatment with foscarnet and resolved after the cessation of the drug. Intravenous enfuvirtide was the second drug for the induction phase. Sensitivity to this drug was tested before the treatment, and the IV form was preferred in order to reach higher trough levels, which was suggested in a previous report to treat resistant HIV.[18] In the present report, an induction regimen comprising, among others, IV foscarnet and emfuvirtide, resulted in an effective reduction of the plasma HIV RNA level at each hospitalization (Figure). However, the viral suppression was not maintained, most likely because of adherence problems. On the other hand, no fully effective oral drugs were available after high-level resistance developed in 2018. Fostemsavir was introduced after study results confirmed fostemsavir activity in treatment-experienced individuals.[6] Fostemsavir resistance-associated mutations were detected in drug-experienced individuals with HIV included in a recent trial.[8] The

Table 2. Evolution of the Resistance-Related Mutations Detected in the Genotypic Resistance Profiles

nRTI							
Linked with resistance to	**AZT**	**Accessory**	**3TC/ FTC/ ABC/ TDF**	**AZT**	**ABC**	**ABC/ TDF/ AZT**	**ABC/ TDF/ AZT**
Wild type	**M41**	**E44**	**K65**	**D67**	**L74**	**L210**	**T215**
Oct 11, 2004	41L	44D	65R	67N		210W	215D
Jun 27, 2008	41L	44D		67N	74I	210W	215Y
Nov 2, 2009	41L	44D		67N	74IL	210W	215Y
Jun 10, 2011	41L	44D		67N	74I	210W	215Y
Nov 17, 2011	41L	44D		67N	74I	210W	215Y
Aug 28, 2012	41L	44D		67N	74IL	210W	215Y
Jan 7, 2013	41L	44D		67N		210W	215HPYS
Aug 31, 2018	41L	44D		67N	74I	210W	215Y
Nov 22, 2021	41L	44D		67N	74I	210W	215C

NNRTI							
Linked with resistance to	**RPV/ NVP**	**DOR/EFV/ NVP**	**(ETR/ RPV not well studied)**	**ETR/ NVP/ RPV**	**ETR/ NVP/ RPV**	**EFV/ NVP**	**EFV/ NVP**
Wild type	**K101**	**V106**	**E138**	**V179**	**Y181**	**G190**	**P225**
Oct 11, 2004	101E	106M			181C	190A	
Jun 27, 2008	101E				181C	190A	
Nov 2, 2009	101E	106MV			181C	190A	
Jun 10, 2011	101E				181C	190A	
Nov 17, 2011	101E				181C	190A	
Aug 28, 2012	101E				181C	190A	
Jan 7, 2013	101E				181C	190A	
Aug 31, 2018	101E		138A	179F	181C	190A	225H
Nov 22, 2021	101E				181C	190A	

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Table2. Evolution of the Resistance-Related Mutations Detected in the Genotypic Resistance Profiles *(continued from previous page)*

PI												
Linked with resistance to	**DRV/ FPV/IDV/ LPV/NFV**	**Highly polymorphic but with DRV resistance**	**Minor, all but SQV**	**Minor, all PI**	**Accessory**	**Minor, all but DRV**	**All but TPV**	**Accessory**	**Minor**	**Major, all**	**Accessory but with R to IDV, NFV, FPV, LPV, and DRV**	**All but TPV and DRV**
Wild type	**L10**	**K20**	**V32**	**L33**	**K43**	**M46**	**I54**	**T74**	**V82**	**I84**	**L89**	**L90**
Oct 11, 2004	10F	20R		33F	43T		54V		82A	84V		90M
Jun 27, 2008	10F	20R		33F	43T		54L		82A	84V		90M
Nov 2, 2009	10F	20R		33F	43T		54L		82A	84V		90M
Jun 10, 2011	10F	20R		33F	43T		54L		82A	84V		90M
Nov 17, 2011	10F	20R		33F	43T		54L		82A	84V		90M
Aug 28, 2012	10F	20R		33F	43T		54L		82A	84V		90M
Jan 7, 2013	10F	20R		33F	43T		54L		82A	84V		90M
Aug 31, 2018	10F	20R	32I	33F	43T	46I	54L	74P	82A	84V	89F	90M
Nov 22, 2021	10F	20R	32I	33F	43T	46I	54L	74P	82A	84V	89F	90M

InSTI						
Linked with resistance to	**Accessory**	**RAL/EVG/ DTG**	**Minor EVG**	**EVG**	**All**	**RAL/ EVG/ DTG**
Wild type	**Q95**	**E138**	**Y143**	**S147**	**Q148**	**N155**
Jun 27, 2008		138K				
Nov 2, 2009		138K				
Jun 10, 2011		138KE				
Nov 17, 2011		138K	143R			
Aug 28, 2012	95K	138K		147G	148QR	155H
Jan 7, 2013	95K	138K		147G	148QR	155H
Jul 30, 2013	95K	138K		147G	148R	155H
Aug 31, 2018						
Nov 22, 2021	95K	138K		147G	148R	155H

Abbreviations: 3TC, lamivudine; ABC, abacavir; AZT, xidovudine; DOR, doravirine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; FPV, fosamprenavir; FTC, emtricitabine; IDV, indinavir; InSTI, integrase strand transfer inhibitor; LPV, lopinavir; NFV, nelfinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitors; NPV, nevirapine; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; SQV, saquinavir; TDF, tenofovir; TPV, tipranavir.

above-mentioned mutations were searched in the samples of the described patient and were not identified. Finally, lenacapavir was added to overcome incomplete viral suppression and seems to have been highly effective in re-pressing this extremely drug-resistant virus, confirming recent studies.[8,19] Susceptibility testing for lenacapavir was not performed, but no pre-existing resistance to lenacapavir has been found in studies, regardless of former treatments.[7,19]

The patient's mental health disorders have hampered the treatment adherence and certainly played a role in incomplete viral suppression. However, the very limited treatment options and, consequently, the burden of ART, have sustained a vicious circle. Gastrostomy, directly observed therapy, and psychiatric follow-up were implemented to improve adherence. The development of easier administration methods than daily oral dosing, as is the case with lenacapavir, may reduce the evolution of resistance in the future.

Conclusion

The well-documented viral genotypic and phenotypic profiles guided clinicians in their treatment strategies over the years and allowed monitoring of the evolution of the HIV-1 strain to 4-class resistance. Highly resistant HIV infection requires a multidisciplinary approach, with practitioners who have extensive expertise in viral infections, mental health problems, and social issues, sometimes leading to unconventional but effective management under close supervision. In heavily experienced individuals with pan-resistant HIV, first-in-class newly available drugs may become an effective strategy to achieve viral suppression.

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