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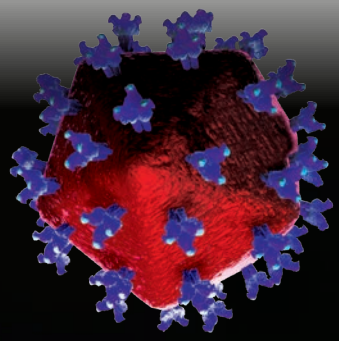

40 Years of HIV

Separating the Signal From the Noise

Are Test Providers Profiteering From The Pandemic?

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40 Years of HIV

Getting the Signal Through the Noise

By Marie Rosenthal, MS

At first, it was a puzzle—a 33-year-old man, formerly healthy with a two-month history of fevers of unknown origin, elevated liver enzymes, oral mucosa candidiasis and cytomegalovirus —who presented to the emergency room at UCLA Medical Center, in Los Angeles, with dyspnea.

He died shortly afterward, and on post-mortem was found to have an unusual pneumonia, caused by *Pneumocystis carinii*—later renamed *P. jirovecii*—which typically affected people who were severely immunocompromised. But there was no evidence of a condition that would have impaired his immune system.

One patient.

An infectious disease curiosity, nothing more.

But then there were others.

In 1981, Michael S. Gottlieb, MD, and his colleagues published what is regarded as the first paper on HIV, which reported on five patients—all young, previously healthy men (*MMWR Morb Mortal Wkly Rep* 1981;30[21];1-3).

"It started with one patient who had something unusual and quickly became several patients, then dozens of patients with unexplained illness," said Dr. Gottlieb, a staff physician at APLA Health in Los Angeles, and an associate clinical professor of medicine at the University of California, Los Angeles Geffen School of Medicine.

Kaposi's sarcoma.
Source: NCI

Dr. Anthony Fauci in 1984.
Source: NIAID

These patients appeared to have nothing in common except their gender and sexual orientation. They came from different socioeconomic backgrounds and shared no known contacts.

They all reported being gay, but only two reported having several partners. All five reported using "poppers," inhaled psychoactive amyl nitrite that was thought might play a role in weakening their immune systems. (Eventually, it was realized that poppers had a role in behaviors that put them at risk [*Ann N Y Acad Sci* 1984;437:192-199]).

Other reports were published of men with unusual conditions, such as *Mycobacterium intracellulare* infection, which typically affects severely immunocompromised people.

One month later, there was a report of 26 cases of Kaposi sarcoma (KS) among homosexual men in New York City and California (*MMWR Morb Mortal Wkly Rep* 1981;30[25]:305-308).

It might have taken longer to put the puzzle together if the cases were not seen in academic medical centers, noted Dr. Gottlieb, an allergist and immunologist, who helped found the American Foundation for AIDS Research with Elizabeth Taylor in 1985, after his AIDS patient, actor Rock Hudson, died.

That first *MMWR* report was published because "it happened at an academic medical center—UCLA—where this first patient stumbled into the emergency room, and then word traveled to the community," Dr. Gottlieb said. After that publication, people began looking at their own patients, and the dots started to connect.

The CD4 T-lymphocyte deficiency in the first patients was identified in the laboratory of Dr. John Fahey at UCLA, and the patients reported in *MMWR* were described in greater detail in December 1981 (*N Engl J Med* 1981;305[24]:1425-1431). "Thus, CD4 was identified early on as the target of a putative retrovirus, suggesting to the Pasteur and other groups that they look for a virus that attacked CD4 cells using cultured CD4 T cells," Dr. Gottlieb said. "CD4 typing was a research tool at the time at UCLA and not clinically available, another reason why being at an academic center allowed these early observations. Identification of CD4 as the target facilitated the discovery of the virus within three years of the initial case reports."

Dr. Gottlieb was on the front line because of his specialty, he explained. It was obvious that the immune systems of these patients were not working. "It was exciting, on one hand, to be involved with something new," he said. "On the other hand, it quickly dawned on me that it was a very serious and probably irreversible immune deficiency."

Powerless Against This New Disease

Cases like these are what intrigues infectious disease specialists, which is why they are called the disease detectives and the people whom specialists call when they've run out of differentials in their own field. The curiosity of many young doctors and researchers was sparked as these reports started appearing.

"I can remember very clearly sitting in my office at the NIH [National Institutes of Health] Clinical Center in June 1981, when the first *MMWR* landed on my desk reporting five young gay men from Los Angeles with *Pneumocystis* pneumonia. I thought that it was either a one-off kind of curiosity or a fluke," said Anthony Fauci, MD, who took time from fighting the COVID-19 pandemic to talk with *Infectious Disease Special Edition*. "I thought maybe they were sniffing some poppers to enhance sexual pleasure or something, but I didn't make much of it."

Then the *MMWR* reported the KS cases, he said, and his interest was piqued. "This time, 26 curiously all gay men, not only from L.A., but now from New York City and from San Francisco, reporting not only *Pneumocystis*, but Kaposi's sarcoma and other opportunistic infections [OIs], and that is when my career and my life changed," Dr. Fauci said, because he realized that "this is a brand-new disease."

Dr. Fauci said that during his ID fellowship and subsequent nine years at the National Institute of Allergy and Infectious

Diseases, he had seen many OIs among chemotherapy patients. For these young men to come down with OIs such as *Pneumocystis* and KS, "something" had to be wreaking havoc with their immune systems.

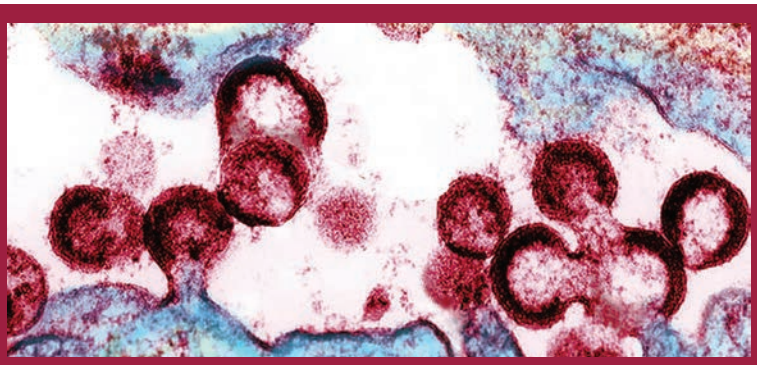
"I made a decision that I was going to totally change the direction of my career. Up to that point, I had been successful publishing in the field of immunoregulation and looking at how the immune system gets suppressed when you give therapies such as prednisone and cytotoxic agents. I said, 'I am going to now start studying this amazingly scary and brand-new disease.'"

This was before the virus was discovered, he reminded.

"My mentors thought I was crazy. They said, 'Why in God's name would you want to divert yourself from a successful career trajectory to start studying a disease in a group of gay men that is probably going to go away and not amount to anything?'" Dr. Fauci recalled.

Another young man, who was studying the link between viruses and cancer, was also intrigued. He had moved to San Francisco to study that connection in the laboratory of Jay A. Levy, MD, one of the discoverers of HIV. "I really liked taking care of cancer patients when I was a medicine resident, and so I decided to have my clinical focus be oncology, although I always planned to still work with viruses in the lab," said Paul A. Volberding, MD, the director of the AIDS Research Institute at the University of California, San Francisco.

"I think, for me, the issue was that it was absolutely new. No one had ever seen anything like this before—it was out of the blue," Dr. Volberding said. "Obviously, it was not the first new disease that people had come across—that's part of the history of medicine—but it was really very remarkable."



Discovery of HIV

One of the more contentious issues surrounding HIV was the discovery of the virus. Drs. Jean-Claude Chermann and Françoise Barré-Sinoussi at Dr. Luc Montagnier's lab at the Pasteur Institute, in Paris; Dr. Robert Gallo at the National Cancer Institute, in Bethesda, Md.; and Dr. Jay A. Levy in San Francisco were looking at human retroviruses. Dr. Gallo had pioneered the detection of RNA viruses with the discovery of interleukin-2 and human T-cell leukemia virus (HTLV).

Each scientist isolated a virus that they believed was the cause of AIDS. Dr. Montagnier identified it as lymphadenopathy-associated virus (LAV); Dr. Gallo called it HTLV-III; and Dr. Levy, AIDS-associated retrovirus (ARV). All of them were correct, and the virus became known as human immunodeficiency virus, or HIV.

Dr. Françoise Barré-Sinoussi in 2008.
Source: Wikimedia Commons

But there was a bitter and very public dispute between the Americans and the French over who first discovered the cause of HIV—a dispute that wound up in court.

In 1987, President Ronald Reagan and French Prime Minister Jacques Chirac reached a joint agreement: They would share scientific credit and patent royalties. However, when the Nobel Committee handed out its 2008 prize for the discovery, it went to Drs. Barré-Sinoussi and Montagnier of the Pasteur Institute.

Donna Mildvan, MD, was an infectious disease physician at Beth Israel Medical Center, in New York City. In the late 1970s, she saw a young man hospitalized with multiple gastrointestinal infections. There was no history of travel, but *Shigella* and *Giardia* were found in his stool, she said.

Then a second patient came into the hospital with a similar pattern. She reported both cases to the city health department, where she met Daniel C. Williams, MD, whose practice brought a perspective on the gay community. "Dan explained that the sexual practices of gay men could have led to the development of these GI infections," said Dr. Mildvan, a clinical professor of medicine at the Icahn School of Medicine at Mount Sinai, in New York. Both patients were gay and had multiple partners.

Drs. Williams and Mildvan collaborated with the CDC to study enteric pathogens as a sexually transmitted infection (STI) and began to notice that many of the men also had unexplained lymphadenopathy. But it wasn't until 1980 that Dr. Mildvan saw her first patient who subsequently was diagnosed with AIDS.

"It was a very unfortunate case of a 33-year-old man who had a series of infections and wasting and eventually died," she said. "You just don't lose a 33-year-old. It was extraordinary."

And like Dr. Gottlieb, a second and then a third patient came in with fulminant disease and died.

"We realized, maybe all that lymph node enlargement we'd been seeing in gay males had something to do with this fulminant manifestation," Dr. Mildvan said. So they began following

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the lymphadenopathy patients longitudinally. "A large number of them progressed to develop AIDS-defining events."

Being around the same age as one's patients—Dr. Gottlieb was 33 when be published that first *MMWR* article—was disconcerting. "I was in my 30s; they were in their 30s. All of our patients died within that first year after diagnosis. It quickly became scary and disheartening to see these men die, and not be able to tell their parents, in some cases, lovers, and others what was wrong with them because we didn't know what had caused their immune systems to fail," Dr. Gottlieb said.

"We were powerless in the face of this new disease," he added.

"I saw my first KS patient literally at my first day on the faculty at San Francisco General Hospital, and the patient was my age. I had just turned 31," Dr. Volberding said. "The patients were coming in in their 20s and 30s with really bad diseases, really bad cancers that tended to be diseases of aging. So nothing prepared us for what looked like an epidemic of cancer appearing in young people.

"We had no clue what was going on at first, and I didn't expect it to be a new virus," Dr. Volberding said, so he had no qualms about caring for these patients. Then the blood transfusion cases started to appear, so it became clear it was an infectious agent.

"That is when it became real to me, and I was really terrified of it because we didn't know the nature of it. We didn't know how it was transmitted. We had no way to diagnose it, and so that was a pretty fraught period," Dr. Volberding said.

It was a time of worry for physicians caring for these men until about 1983-1984, Dr. Gottlieb agreed. Several doctors treating HIV/AIDS patients reported unexplained illnesses. Dr. Gottlieb had a scare when he developed a mononucleosis-like illness that lasted a couple of months with extreme fatigue and low-grade fever. "It was before there was an HIV test, so I traveled to Paris, where virologists Jean-Claude Chermann and Françoise Barré-Sinoussi cultured my blood for HIV, because I was concerned about this unexplained illness," Dr. Gottlieb said. Fortunately, the result was negative.

Dr. Mildvan had her own HIV scare. "We were afraid when we realized that it was transmissible," she said. "At one point, I looked at my arm and there was a funny lesion on it, and I thought, 'Oh, God, it's Kaposi sarcoma.'" It faded eventually, and she finally remembered her cat using her arm as a launching pad. "Just about everyone has a story like that," Dr. Mildvan said.

In 1982, the CDC published a case definition, calling the disease "acquired immunodeficiency syndrome (AIDS)" (*Morb Mortal Wkly Rep MMWR* 1982;31[37]:507-508; 513-514), and by 1983, the virus was isolated, which changed everything, because now there was a target for diagnostic tests and treatments.

With a test, the physicians felt safer, because they could at least find out if that odd headache or malaise was HIV. However, needlesticks were a concern; they were rare, but they still occurred, the expert said.

Universal precautions would not be put into place until 1984, and they were implemented largely due to HIV, according to the CDC.

Early Patient Management

The story of HIV/AIDS is more than a story of medical advancement. It is a story of fear, activism, education, disparities and prejudices. It is the story of a pandemic that has spanned 40 years,

Difficult but Important Conversations

When the second patient with multiple enteric diseases presented to Donna Mildvan, MD, and reported he was gay and had more than one partner, she realized she had to go back to the first patient and ask about his sexual behavior—a difficult doctor–patient conversation in the 1970s.

"I had never thought to ask these questions. We would take sexual histories from patients who presented with venereal or sexually transmitted diseases, but nobody really made the connection that amebiasis or *Shigella* or *Campylobacter* could be a sexually transmitted disease," she said. "These were enteric GI diseases that you get from travel or contaminated food."

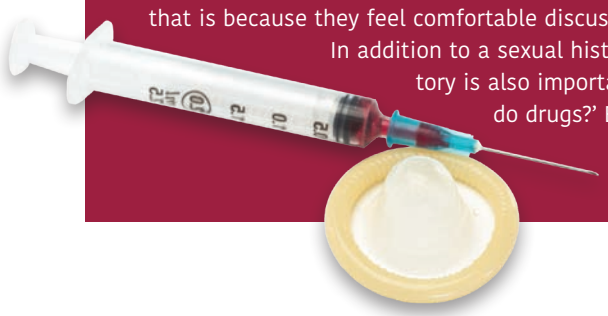
Dr, Mildvan's team reported the cases (*JAMA* 1977;238[13]:1387-1389), and an accompanying editorial emphasized the importance of inquiring about sexual preference in the workup of these patients.

"Back then, this was news," she said.

Today, Julia Garcia-Diaz, MD, MSc, teaches medical students how to have these awkward conversations with patients. "It's not just getting a sexual history," said Dr. Garcia-Diaz. "[They need to know] how to talk to the patient. You need to feel comfortable with the things that you're asking your patients. How many partners, and beyond that, are they male or female? Is it both?

"Now some patients share a little more than I would like," she joked, but that is because they feel comfortable discussing these issues.

In addition to a sexual history, a thorough drug history is also important. "It's not just 'Do you do drugs?' But, 'Do you use needles or share them? How do you cook your meth?'" she said.



infected 79.3 million people and killed almost 40 million. It is a story of life and death.

In the first two years, AIDS appeared to be a problem of gay men, so the public did not give it much attention. However, many of these men were already isolated, often estranged from family and friends because they were gay, and AIDS added to the stigma.

"There was nothing so heartbreaking as watching patients with AIDS in those early days suffer and die," said Paul Sax, MD, who was a medical student when HIV was discovered. "The combination of the absence of effective therapy and the societal stigma and isolation they felt—it really tore you up and you wanted to do everything you could for them."

He remembered one patient who epitomized the early isolation some patients felt. He had come from Cuba with the Mariel boatlift in 1980, and he was dying of AIDS. "He had no family, and he wouldn't tell his friends, so he gradually became more and more isolated," Dr. Sax explained.

When cases occurred in men who were not gay, women, infants or children, Americans started to take notice, and they were afraid, which isolated AIDS patients even more.

An early AIDS testing kit in1985. Source: FDA

One of the most notable patients outside the gay community was an Indiana teenager with hemophilia. In 1985, Ryan White contracted AIDS from a blood transfusion, and fear drove his expulsion from middle school. Ryan and his parents ended up moving to another town because of the bigotry he encountered, and he spent the rest of his short life teaching people about HIV/AIDS. He died in 1990. That year, Congress enacted the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act, which is the largest federal program focused on providing HIV care and treatment services to low-income people living with HIV. (For more on the Ryan White program today, see bit.ly/31Ld6L4-IDSE.)

"The Ryan White Care Act created a pathway for the federal support of AIDS care across the country ... similar to the way the government covers dialysis treatments," Dr. Volberding said.

The occurrence of HIV outside the gay community led to another milestone: the Social Security Administration's decision to allow people with AIDS to apply for disability benefits, according to Julia Garcia-Diaz, MD, MSc, an associate professor, University of Queensland/Ochsner Clinical School, Oschsner Health, in New Orleans, who began providing care for patients in the early 1990s as a medical student. These benefits are important today because they keep people on treatments that could be expensive, Dr. Garcia-Diaz noted. But it was even more important then, when patients became so sick they could no longer work, she stressed.

Even within the hospital, some staff were reluctant to interact with HIV patients. They didn't even want to enter the room to deliver or pick up food trays. Some surgeons refused to do surgeries for these patients.

"Back then, if you referred a patient with HIV for cardiac surgery or orthopedic surgery, you had to choose your surgeon very carefully, because most of them didn't want to do it," Dr. Sax explained. "They didn't want to do it for a combination of their own personal risk—and I don't want to diminish that, they had more personal risk than we did—but they also felt, 'What's the point?' The average life expectancy of someone with AIDS in 1986 was 12 months.

"Today, they want to operate on everyone [with HIV]," said Dr. Sax, which just demonstrates the strides made in HIV care and education.

"Whenever there is a new disease and there is uncertainty about how it's transmitted, I think the public and medical professionals—who are just like other people in terms of worry—will initially be concerned about whether they may be at risk," said Rajesh T. Gandhi, MD, the director of HIV Clinical Services at Massachusetts General Hospital, in Boston, and the past president of the HIV Medicine Association. Dr. Gandhi was a medical resident in the 1980s.

Dr. Gandhi added that, soon after the discovery of HIV, he was reassured by the fact that people with HIV who lived in a household with others who were not sexual partners did not infect their relatives and friends. "So, obviously, eating, drinking and being in a family is typically a closer interaction than being a person's doctor, and that reassured me in those early days after HIV was discovered," Dr. Gandhi said.

Education and communication were crucial, they all said.

All on the Same Team ... Almost

The signal-to-noise ratio—a measurement from radio engineering that separates the noise-free radio signal from background white noise—serves as a good analogy for the early days of HIV on many levels, from discerning the transmissible agent to figuring out how that agent was transmitted and getting research funding.

The fact that most patients were gay, and there was bigotry surrounding same-sex relationships, made them easy for the

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establishment to ignore. And gay people were getting fed up: They wanted answers faster than their friends and lovers were dying, and they weren't getting them.

"It was hard to work. It was hard to get money. It was hard to generate any empathy from the public, and the Reagan administration chose to leave these people behind," Dr. Gottlieb said.

"The gay community was deathly afraid," Dr. Volberding said, "and that fear translated into anger when the community felt that not enough was being done to help understand it [the disease]. It took a while for the research grants to start moving."

Groups such as ACT UP (AIDS Coalition to Unleash Power) and The Gay Men's Health Crisis were crucial in getting those research grants, as well as being integral partners in HIV research, they said.

In addition to demonstrations in cities around the world, activists also were a vocal presence at the AIDS medical conferences. Several people interviewed for this story told about presentations being disrupted by activists, of speakers at the podium when demonstrators entered and threw symbolic blood—red paint—on them, and researchers who had guards outside their hotel room doors during the conference because they were afraid. Dr. Mildvan thought some of that anger, disruption and theater was misdirected at the physicians and researchers who were just trying to help.

"Those of us who were working in HIV became to some degree the heroes, but also to some degree the villains," Dr. Volberding explained. "We were seen as complicit with the government in not responding adequately because we weren't able to do anything. We couldn't cure the disease."

But there was also unity.

During the Sixth International Conference on AIDS in San Francisco, protesters drowned out then Health and Human Services Secretary Louis W. Sullivan, MD, while he was delivering the closing address. Dr. Mildvan remembers all of the physicians also turned their back on him, and everyone was shouting.

"Everybody, to a person, all the delegates were on our feet with our backs turned to the stage where he was trying to speak," Dr. Mildvan said. "It was just so loud and so overpowering, and everybody was unified in our dismay at what the government had been doing—or not doing—with Sullivan as the representative.

"So, we were grateful to the activists because as delegates, we would not have protested without them," she said.

"Their [AIDS activists'] role was huge in moving the ball forward," Dr. Gottlieb said. "Larry Kramer and his associates were prophets in their day, said things that other people

An ACT-UP organized protest outside of the FDA's headquarters in Rockville, Md., in 1988. Source: FDA

didn't want to hear about safe sex, and ACT UP was incredibly important in getting to where we are now—in pushing the federal government, the NIH to study treatments for people with HIV and liberalizing access to experimental therapies."

Dr. Fauci was one person who was instrumental in bringing the communities together, several people said, and brought the gay community, pharmaceutical companies and the government together as partners in research. He worked with activists and changed the way clinical trials were done to include patient input. He also helped them get access to experimental drugs and helped speed up the approval process within the FDA.

In 1984, he became the director of the National Institute of Allergy and Infectious Diseases, where he made sure HIV was a major research concern. He was also instrumental in developing the plan, "Ending the HIV Epidemic in the U.S.," in 2019 (bit.ly/3pLfn1n-IDSE).

"At first he was criticized by activists, but then he worked together with activists in a very meaningful way," Dr. Gandhi said.

"I have to hand it to Tony Fauci, because he partnered with them rather than excluded them," Dr. Sax added.

"The signal-to-noise finally got through as a signal, and they made all the difference once they arrived. They made an enormous amount of contributions," Dr. Mildvan explained.

Breakthroughs and Challenges

Azidothymidine (AZT), also known as zidovudine, developed for HIV by Burroughs Wellcome, was approved in 1987—25 months after demonstrating activity against HIV in the lab—one of the shortest periods of drug development until COVID-19. It did not prevent viral replication, but slowed the progression to AIDS.

"It was a groundbreaker because it was the first effective

COVID-19 Versus HIV *By Marie Rosenthal, MS*

Because they are both viral pandemics, COVID-19 was compared quite a bit with HIV, especially in the beginning of the pandemic. Both are seeing a high morbidity, but is that where the similarities end? The answer is yes and no.

"Well, they're both viruses, but apart from that, they are very different," said Paul Volberding, MD, of San Francisco. "The epidemiology is completely different. What we learned is that COVID-19 can, but rarely, kills people, and HIV always kills people. HIV is very difficult to transmit; COVID is very easy to transmit. Everyone is susceptible to COVID, and most people have no great risk for HIV, even before treatments were developed just by nature of how the virus is commonly transmitted."

Michael S. Gottlieb, MD, agreed: "The modes of transmission are so different. HIV resembles type B hepatitis in its transmission, whereas COVID-19 represents common respiratory viruses. COVID-19 affects everyone. Theoretically speaking, everyone is at risk for HIV, but only through certain routes of transmission. COVID-19 is out there for everyone to contract," said Dr. Gottlieb, of Los Angeles.

The high mortality rates are certainly similar, but the time line is very different, with HIV killing millions over 40 years, and COVID-19 killing millions in just two, said Jonathan Z. Li, MD, of Boston, but there is more stigma attached to HIV—even today—because it is a sexually transmitted infection.

However, the groundwork set for a drug approval during the early days of HIV was certainly used during COVID-19, "allowing the FDA to be more flexible in a time of emergency. Without those early HIV activists pushing against the initial, ossified way that the FDA used to do things, I'm not sure that they would be able to be as nimble as the FDA and the U.S. government have been for the current pandemic."

The treatments have a commonality, too, he said. "Some of the vaccines and treatments for COVID-19 were built on a foundation of HIV research," Dr. Li said. "If you look at the J & J vaccine, that was an adenoviral-based vaccine that was developed in Dan Barouch's lab and built off of a platform that he's been studying for 20 years for HIV vaccine. There's no way that that vaccine could have been created in such a short time frame without the two decades of research that had gone into it as part of HIV research."

In addition, the research in neutralizing antibodies that has been done for HIV treatment led to monoclonal antibodies, and Pfizer is working on a protease inhibitor, another HIV technology, for COVID-19.

The biggest difference is the time line, according to Julia B. Garcia-Diaz, MD, of New Olreans. "HIV lasted for years and years, and COVID was rapid, and so the time line was very different," she said.

"These are different times with different technology. I think that we did things for HIV as quickly as we could have done it, but that is a span of 15-plus years; research did not start until the mid-, late 80s. We did not have HAART [highly active antiretroviral therapy] until about the mid-90s, and here we have remdesivir within six months. [In contrast,] COVID just spread like a wildfire throughout the world," Dr. Garcia-Diaz said.

So many infectious diseases are diseases of poverty and vulnerable populations, such as HIV and tuberculosis, observed Dr. Rajesh T. Gandhi, MD, of Boston, and COVID-19 highlighted that by disproportionately affecting vulnerable populations. "I don't think we learned the lesson, though."

Both are global infections. "I think it's highlighted to the extreme with COVID, but this idea that we can attempt to treat HIV here and not be concerned about it globally. ... In the late 1990s, it became clear that it just was totally unethical to have treatments that were available to Americans, but not to people in resource-limited settings," he said.

COVID-19 has had a direct effect on the HIV pandemic, however, in that many resources were diverted from HIV research and care to the COVID-19 response, they said.

This is especially true for the federal plan for ending HIV in America, Anthony Fauci, MD, admitted. "Well, I think COVID has upended everything everyone does on the planet," he said. "So, you can't say it hasn't interfered with the plans to end HIV because it interfered with access to health care on the part of some people who otherwise would get tested and put on therapy early, [and] it interferes with people getting the counseling that gets them into PrEP or pre-exposure prophylaxis.

"It interferes in the developing world who has supply chain issues of getting drugs to people. So, I think anyone who has anything that requires a stability in society has actually been upended," he said.

"The impact of COVID on HIV, TB, malaria and probably every aspect of medical care has been substantial," Dr. Volberding said. People have decreased their uptake of PrEP; there is less testing; and it probably has affected adherence because patients were not seeing their physicians regularly.

"I think that COVID has delayed research in all areas," Dr. Garcia-Diaz added. "HIV research has slowed down because the big companies have diverted their focus to COVID-19 [therapeutics and vaccines]."

And money for research is finite, she reminded, "very finite."

drug," Dr. Fauci said. "We had nothing before AZT. It saved a lot of lives. It wasn't a durable effect in most people, but it saved a lot of lives."

Dr. Volberding agreed. "The fact that it wasn't very potent is almost not as important as that it opened the door. It did not reverse the disease, but it slowed it down."

Dr. Gandhi added that one of most important contributions of AZT was that it gave patients hope.

Treatment took a huge leap forward again in 1996, with research presented at the Vancouver International AIDS Conference on combination antiretroviral therapy.

It was not only groundbreaking, it was thrilling, according to Dr. Sax, who quickly saw the benefits of treatment in his patients. "The treatment group made remarkable recoveries. Patients who had lost 30, 40 pounds and looked as if they were at death's door, within six to eight to 12 weeks they gained weight, put color in their cheeks and went back to work. Wow."

Today HIV is a very different disease from what it was 40 years ago because it is considered a chronic condition, not a death sentence. There have been so many breakthroughs in treatment—preexposure prophylaxis, one-pill-daily treatments and injectables that last weeks between doses—and all with fewer adverse events. Many of these treatments make viral loads so low they are undetectable, and undetectable means untransmissible, Dr. Fauci reminded.

"The pills are much smaller, the regimens are more tolerable, and the side effects are better," Dr. Garcia-Diaz said.

"HIV in my mind is very dynamic and the treatments are continually evolving," Dr. Gandhi said. "They've gotten better and better since those days of AZT."

But there is still much work to be done, and many challenges lie ahead, they said.

"We want the cure," said Dr. Garcia-Diaz, who is a member of the *Infectious Disease Special Edition* editorial advisory board. "I don't know if it is going to be in my lifetime, but I am hoping that I could have that conversation with my patients, 'Hey, this is the pill that is going to cure you,'" she said.

"I'm an optimistic person," said Jonathan Z. Li, MD, an associate professor of medicine at Harvard Medical School and the Brigham and Women's Hospital, in Boston. "First of all, there have already been a couple of instances of HIV cures, but of course, both of those instances required a bone marrow transplantation, which has a high up-front mortality, so it's not broadly applicable. But it is a proof of principle that HIV cure is possible."

Dr. Li, who also is a member of the *Infectious Disease Special Edition* editorial advisory board, studies elite controllers—those HIV patients who control viral replication without antiretroviral therapy—and hopes they will help promote cure research. The Esperanza patient, an elite controller who appeared to have cleared HIV without antiretroviral therapy, is a very exciting development, he said (*Ann Intern Med* 2021 Nov 16. https://doi.org/10.7326/L21-0297). Researchers are taking a close look at her cells to see if that information could translate to treatment and the eventual cure of HIV infection.

Dr. Li began his medical career in the 2000s—later than the other physicians interviewed for this story—but he said his early work spent in Mexico and China gives him a better understanding of what patients and physicians were going through in the early 1980s. "Those were regions of the world you still saw stigma and lack of access to care and end-stage HIV, and the kind of desperation of the patients [that was seen in the United States in the 1980s]," he said.

It also helped him to understand the importance of making sure that breakthroughs in the West make it to developing countries.

"These are challenges, but also opportunities," Dr. Li said. "One pill once a day for the vast majority of patients is phenomenal, but making sure that these pills are available around the world, including sub-Saharan Africa, where the vast majority of patients are, I think that is a priority."

Dr. Gandhi agreed. "We need to give equal attention to making sure there is equitable distribution of life-saving technologies," he said.

Vaccination is another challenge, they said, but one that still has a lot of interest, despite disappointing results in the past. As *Infectious Disease Special Edition* was going to press, there was a report that the messenger RNA technology used for the COVID-19 vaccines was successful in preventing simian immunodeficiency in primates (*Nature Med* 2021 Dec 9. doi:10.1038/s41591-021-01574-5). So, there is some hope in that area, too.

Despite all the education and knowledge, there is still stigma attached to being gay and having HIV, Dr. Sax said. "It is maddening," he said, that some patients still won't take their medications because of that stigma. "I think if the stigma was removed completely, they would be able to do it because they take their medicines for other conditions, but they just don't take their HIV medications."

Despite all the challenges, not one physician interviewed for this article said they were sorry they went into the field of HIV. They all agreed that caring for this special group of patients is its own reward.

Yet, all of the early pioneers in HIV, who have treated thousands of patients, remember those early young men who started them on their career paths, and those first patients are particularly special, the early HIV doctors told *Infectious Disease Special Edition*.

"The patients trusted us," Dr. Gottlieb said. "We had a bond with them. Those first patients I remember better than the patients I saw last week. I remember them by name, and I remember their faces.

"And people still tell me they remember where they were when they read that first report," he said. ■