



A HALF-CENTURY OF PROGRESS IN HEALTH: THE NATIONAL ACADEMY OF MEDICINE AT 50

## Four Decades of HIV/AIDS — Much Accomplished, Much to Do

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The dramatic saga of the acquired immunodeficiency syndrome (AIDS) features an early sense of helplessness and frustration in the face of a mysterious new disease, courage on the

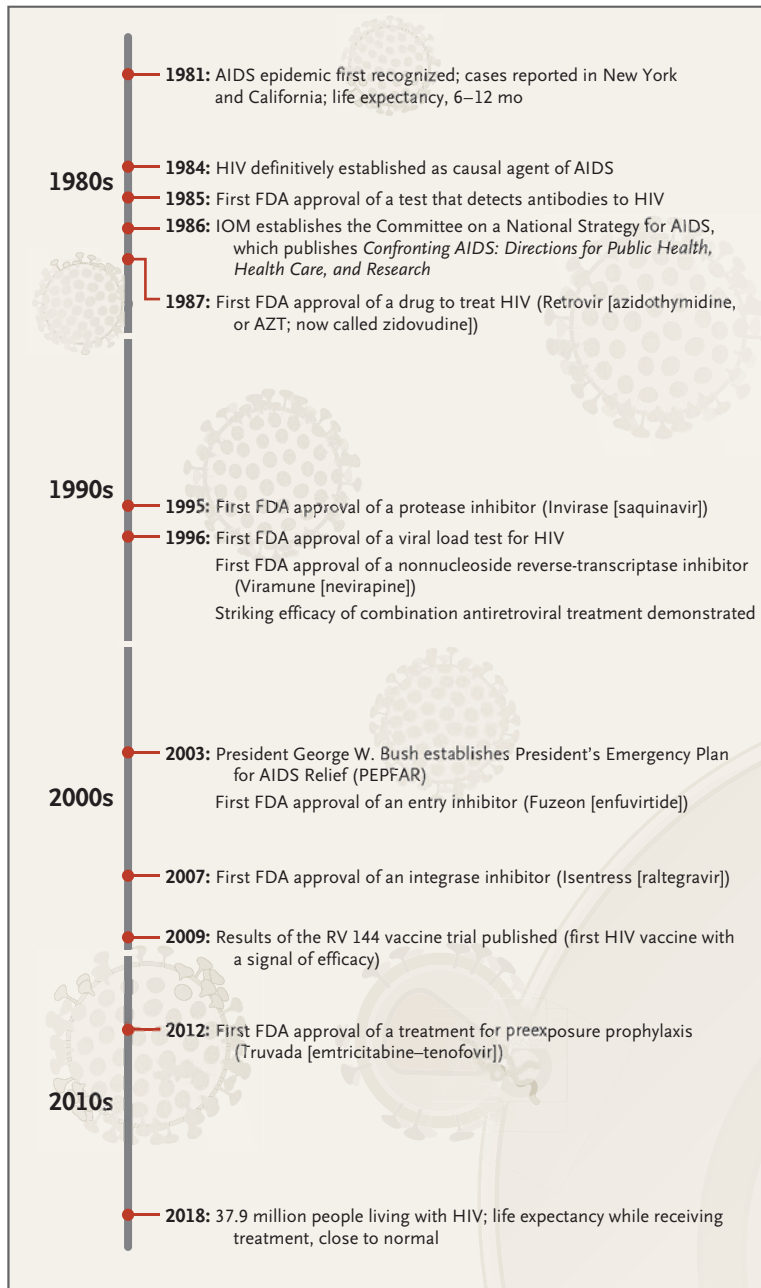
part of the afflicted, and the gradual accrual of groundbreaking scientific advances that have brought hope to a formerly desperate situation. This progress began with a series of detailed epidemiologic studies, which were followed by the discovery of the human immunodeficiency virus (HIV) as the causative agent of AIDS, and has culminated in highly effective treatment regimens that have transformed HIV from a near-certain death sentence to a manageable disease (see timeline). Looking ahead, and considering the spectacular sci-

entific advances that have been made over nearly four decades, it is conceivable that with optimal implementation of available prevention strategies and treatments, the end of HIV/AIDS as a global pandemic will be attainable.

This extraordinary journey began in 1981 with the initial reports of the first recognized case of AIDS in the United States. During the early years of the outbreak, the disease did not have an agreed-upon name and the causative agent of the new syndrome had not yet been identified. As a result, there were no

specific medications available to treat patients with the syndrome, and their life expectancy was measured in months. Coinfections and neoplasms associated with the unknown disease resulted in high mortality.<sup>1</sup> Health care providers could offer little to the multitude of patients flooding into clinics and occupying a disproportionate fraction of hospital beds in large cities such as New York, San Francisco, and Los Angeles.

The Institute of Medicine (IOM — now the National Academy of Medicine, or NAM) of the National Academy of Sciences, which is now celebrating its 50th anniversary, played a key role in the early response to AIDS, notably with the establishment in 1986 of the Committee on a National



**Progress against the HIV/AIDS Epidemic.**

Strategy for AIDS, which published the seminal publication *Confronting AIDS: Directions for Public Health, Health Care, and Research*. This volume served as a road map and rallying call for policymakers, scientists, and others to address the growing pandemic in all

its complexities. Over the ensuing years, the IOM/NAM has continued to provide leadership and expertise on HIV/AIDS.

The first glimmer of hope that medicine might be able to mount an effective response to this frightful plague came with the inde-

pendent discovery — by the laboratories of Luc Montagnier and Robert Gallo — of HIV as the causative agent of AIDS.<sup>2,3</sup> This advance led to the development of diagnostic assays that provided, for the first time, insight into the true scope of the outbreak. It became clear that patients presenting with advanced disease were just the tip of the iceberg and that orders of magnitude more people globally were living with HIV infection but had not yet developed obvious clinical disease. Building on these initial studies, researchers studying the epidemiology and natural history of HIV provided a snapshot of the full scope of a global epidemic.

Scientists also began to delineate the complex aspects of the HIV replication cycle and the pathogenic mechanisms of HIV disease, including the relationships among viral load, CD4+ T-cell count, and the full range of disease complications. Notably, understanding the intricacies of the HIV replication cycle led to the identification of vulnerable targets for intervention by antiretroviral agents.

In 1987, the antiretroviral drug azidothymidine (AZT; now called zidovudine), an inhibitor of the viral reverse transcriptase, was licensed; it provided a temporary reduction in the amount of HIV RNA in the blood and a modest improvement in the health of people with HIV. The single-drug treatment regimen was followed by two-drug therapy in the early and mid-1990s that resulted in better, but still incomplete, suppression of virus. This period saw an unprecedented engagement of the patient and activist communities in the research agenda and in the process of drug availability

— engagement that led to making AZT available before formal licensure through a treatment IND (Investigational New Drug), the precursor to today's Emergency Use Authorization.

The next landmark advance was transformational: highly effective combination antiretroviral therapy (ART) with three-drug treatment regimens, including the recently developed protease inhibitors or nonnucleoside reverse-transcriptase inhibitors, that durably suppressed the level of virus below the limit of detection by sensitive assays.<sup>4</sup>

With the advent of highly effective combination ART in 1996, efforts to counter HIV on both the individual and population levels entered a new era. ART led to dramatic improvements in the health of individual patients with already advanced disease and to prevention of disease progression in those without obvious clinical manifestations of HIV disease. Not only did ART provide a nearly normal life expectancy for most people with HIV who adhered to their treatment regimens, it also eliminated the risk of transmitting the virus to an uninfected sexual partner.<sup>5</sup> It became clear that treating people with HIV was a highly effective means of preventing HIV spread. "Treatment as prevention" proved to be a critical addition to the prevention tool kit that also contained measures such as condom use, voluntary medical male circumcision, and screening of the blood supply. Studies of these interventions also provided the critical evidence base for the principle that "undetectable equals untransmittable," or "U=U," which has helped reduce some of the external and sometimes self-imposed

stigma associated with HIV infection.

A second major advance in using ART to prevent HIV infection was the introduction of preexposure prophylaxis, or PrEP, for at-risk but uninfected people. Numerous studies have led to the conclusion that a once-daily, single-pill PrEP regimen is 99% effective in preventing sexual acquisition of HIV infection by an at-risk uninfected person. This overwhelming evidence resulted in the U.S. Preventive Services Task Force Grade A recommendation that PrEP should be offered to all persons at high risk for acquiring HIV infection.

Despite these major scientific advances, serious challenges remain in addressing the global HIV/AIDS pandemic and ultimately bringing it to an end. The Joint United Nations Program on HIV/AIDS (UNAIDS) reports that at the end of 2018, a total of 37.9 million people globally were living with HIV. In that same year, 1.7 million people became newly infected with HIV and 770,000 people died from AIDS-related illnesses ([www.unaids.org/en/resources/fact-sheet](http://www.unaids.org/en/resources/fact-sheet)). These daunting figures underscore the fact that much still needs to be done — such as developing a safe and effective HIV vaccine, developing long-acting antiretrovirals, including broadly neutralizing antibodies for prevention and treatment, and identifying strategies for eradicating HIV (achieving a "cure").

In addition, it is imperative that we maximally implement the highly effective prevention and treatment tools already available to us. In this regard, substantial progress is being made through the transformative programs supported by the President's Emergen-

cy Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis, and Malaria. These programs have worked closely with host-country governments in achieving a marked decrease in the number of new HIV infections, an increase in the numbers of persons with HIV accessing ART and achieving viral suppression, and the scale-up of essential health system infrastructures capable of also addressing other health problems. As of September 30, 2019, PEPFAR had provided HIV testing to 79.6 million people; provided ART to 15.7 million men, women, and children; and enabled 2.6 million uninfected babies to be born to mothers with HIV ([www.state.gov/wp-content/uploads/2019/11/PEPFAR-Latest-Results\\_WAD\\_2019.pdf](http://www.state.gov/wp-content/uploads/2019/11/PEPFAR-Latest-Results_WAD_2019.pdf)).

A PEPFAR-like program has also been undertaken in the United States. "Ending the HIV Epidemic: A Plan for America" ([www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview](http://www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview)) is designed to increase HIV testing and diagnoses, provide people with treatment rapidly so that sustained viral suppression can be achieved, prevent at-risk persons from acquiring HIV infection, and rapidly detect and respond to emerging clusters of infection. Achieving the initiative's goal of reducing the numbers of new infections in the United States by 75% over 5 years and by 90% within 10 years requires optimal implementation of current evidence-based prevention and treatment strategies. In addition, we need to overcome barriers inherent in the health care system and other aspects of society that limit access to high-quality care. In this regard, the multisector "Get-

ting to Zero” initiative in San Francisco is providing proof of the principle that eliminating HIV infections and deaths as well as HIV-related stigma and discrimination is feasible. This project could serve as a model for implementation of a combination of treatment as prevention and PrEP at the local, regional, national, and global levels.

The challenge before us is to deploy — for everyone who needs them — the innovative strategies for HIV prevention and treatment that have resulted from the unprecedented basic scientific and clinical advances made over the past four decades. These transformative achievements have resulted from the marriage of basic and clinical research and unusual collabora-

tions at the national and global levels among academia, government, industry, and civil society, including people with HIV/AIDS. We believe that these collaborative efforts must continue to be nurtured and sustained. Progress continues in evaluating new approaches, as demonstrated by two ongoing large-scale clinical trials of HIV vaccine candidates. The goal of our historic four-decade-long journey to end the global HIV epidemic, however, will be reached only when we have a safe and effective vaccine and have addressed the remaining implementation challenges.

The series editors are Victor J. Dzau, M.D., Harvey V. Fineberg, M.D., Ph.D., Kenneth Shine, M.D., Samuel O. Thier, M.D., Debra Malina, Ph.D., and Stephen Morrissey, Ph.D.


Disclosure forms provided by the authors are available at [NEJM.org](http://NEJM.org).

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 An audio interview with Dr. Fauci is available at [NEJM.org](http://NEJM.org)

## Age, Complexity, and Crisis — A Prescription for Progress in Pandemic

Louise Aronson, M.D.

It's a sunny Sunday in San Francisco as I tackle overdue clinic notes and Covid-19 sweeps the planet. I am scheduled to speak in 10 other states over the coming weeks, and as a healthy, middle-aged physician from a region with growing numbers of infections, I'm as likely to be a vector as a victim. Over the next 48 hours, I or my hosts will cancel all my long-planned trips. Meanwhile, I obsessively check the news, trying to decide the safest course of action for me, my family, my patients, and my fellow human beings around the globe.

Surprisingly, what gives me greatest pause has nothing to do with the pandemic — at least overtly. I fear that a septuagenarian patient's recent hospital stay is a harbinger of what may befall older adults throughout the country during the pandemic, even as I hope her experience might serve as inspiration for much-needed health system improvements. Already, I'm acutely aware of the perverse poignancy with which the outsized impact of Covid-19 on elders has laid bare medicine's outdated, frequently ineffective or injurious approach to

the care of patients who are the planet's fastest-growing age group and the generations most often requiring health care.

Reviewing Sally's chart (she insists that I call her by her first name), I learn about her many visits and e-messages to our medical center over the weeks leading up to an elective, come-and-go procedure that turned into a 4-day hospitalization. I'd only had time to glance through her chart before her serendipitously scheduled routine follow-up geriatrics consultation with me a few days after her discharge. Now I read