SPECIAL ISSUE: **IMMUNOTHERAPY AND INFECTIOUS DISEASE** | CONFERENCE COVERAGE: **AACR | AMCP | COA | ISPOR**

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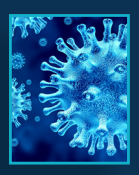
SUPREME COURT: Government Owes ACA Insurers $12 Billion, SP158.

UNPREDICTABLE AND INEVITABLE. The message from our Chairman draws the connections between the seeds planted by HIV research in the 1990s to modern advances, including chimeric antigen receptor T-cell therapy, SP138.


FABRIZIO

ADDRESSING THE GAPS. Fully realizing the potential of immunotherapy requires addressing the limits of the current precision medicine infrastructure. Can the use of tumor mutational burden fill the gaps? Foundation Medicine's David Fabrizio weighs in, SP146.

FROM OUR COVERAGE OF AACR: COVID-19 Increases Overall Risk of Death, Complications in Patients With Cancer, Study Shows, SP148.



FULL COVERAGE OF COA. The Community Oncology Alliance's virtual meeting drew nearly 5000 followers for 2 days of sessions. See full coverage of clinical and business sessions, including an assessment of the state of telemedicine and a call to bring clinical trials closer to patients, SP151-SP156.


PATEL


BURRIS

COMMENTARY

How to Optimize Cancer Therapy When Coronavirus Hits the Fan

Afsaneh Barzi, MD, PhD and Sarmad Sadeghi, MD, PhD

JANUARY 2020 MARKED ONLY the beginning of public awareness about coronavirus disease 2019 (COVID-19) in the United States and around the world.[1] At that point, the idea that the virus would impact this country with the magnitude it has was unimaginable. Similarly, thinking that a virus could play a role in decisions about cancer therapy was inconceivable for any of us on the front lines of treating cancer patients. Cancer is and will continue to be a major cause of mortality in the United States and around the world. Typically, noncancer issues take a back seat when dealing with patients with cancer. But…maybe not this time! Limited data from China suggest that those with cancer have a higher likelihood of death from COVID-19 than those with other comorbid conditions.[2] What can we do to protect our patients with cancer to give them the best chance for survival?

The American Society of Clinical Oncology recommends that cancer survivors who have completed their treatment and are under surveillance with no known evidence of disease are to be kept out of care facilities.[3] Oncology surveillance evaluations should be postponed until after the crisis is over. We should reassure these patients that staying at home and following public health guidelines are the best option during this crisis. These survivors should be advised against visiting the emergency department (ED) for issues that can be resolved by phone or telemedicine.

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INTERVIEW

Zaia Draws on Decades of Innovation in Infectious Disease for Breakthroughs in Gene Therapy

Interview by Maggie L. Shaw

HOW DID DISCOVERIES IN HIV research lead to the revolution of immuno-oncology? To understand this path, *Evidence-Based Oncology*™ spoke with John A. Zaia, MD, the Aaron D. Miller and Edith Miller Chair in Gene Therapy at City of Hope, a comprehensive cancer center. He also serves as director of its Center for Gene Therapy and is program director of the City of Hope Alpha Stem Cell Clinic, which is funded by the California Institute for Regenerative Medicine.

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PERSPECTIVE

Humility and Hope: Evolution of the HIV Pandemic, From ART to Today's Cancer Cures

Joseph Alvarnas, MD

BIG THINGS HAVE SMALL BEGINNINGS.[1] On June 5, 1981, a report published in *Morbidity and Mortality Weekly Report* described 5 previously healthy young men with *Pneumocystic carinii* (now *P. jiroveci*) pneumonia who, following case review by regional monitors from the CDC, seemed to have "cellular-immune dysfunction related to a common exposure."[2,3] The Epidemiology Intelligence Service officer investigating these patients postulated that this represented "a 'disease acquired through sexual contact.'"[3] Over the next year and a half, similar reports would emerge from San Francisco, New York, London, and Paris.[3-6] By late August 1981, the CDC had described 108 similar cases that now also included aggressive presentations of an uncommon cancer, Kaposi sarcoma.[6] As more case reports accumulated worldwide, there was increasing evidence for a transmissible agent responsible for these growing clusters of severely immunocompromised patients. In September 1982 the CDC used the term acquired immunodeficiency syndrome (AIDS) for the first time to describe the condition.[6] This publication also included the first case definition for AIDS.[7] By April 1984, the retrovirus responsible for AIDS was finally identified.[8] By the end of the decade, 100,000 cases of patients with AIDS had been reported in the United States.[9]

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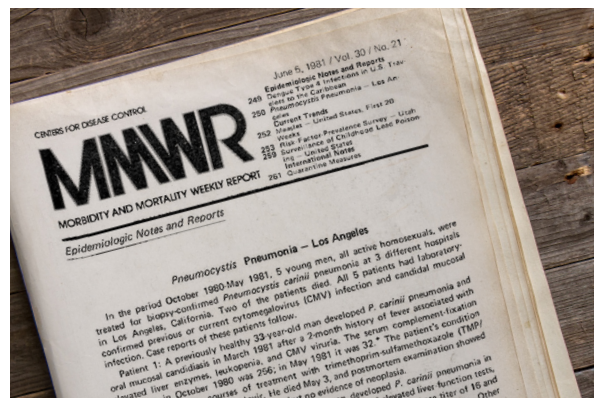
CENTERS FOR DISEASE CONTROL
MMWR
MORBIDITY AND MORTALITY WEEKLY REPORT
Epidemiologic Notes and Reports
June 5, 1981 / Vol. 30 / No. 21
Pneumocystis Pneumonia — Los Angeles

The first report on cases that came to be known as AIDS in the *Morbidity and Mortality Weekly Report*, June 5, 1981.

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PERSPECTIVE

Humility and Hope: Evolution of the HIV Pandemic, From ART to Today's Cancer Cures

Joseph Alvarnas, MD

ALVARNAS

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CONTINUED FROM COVER

The origins of the human immunodeficiency virus (HIV)/AIDS pandemic, however, far precede the initial 1981 case reports. A phylogenetic analysis of HIV-1 points toward a species jump as the initiating event of the pandemic. A variant of the simian immunodeficiency virus found in a subspecies of chimpanzees (*Pan troglodytes verus*) displays striking similarity to HIV-1.[10] This analysis proposes that multiple jumps from simian to human hosts occurred sometime in the late 19th to early 20th century, most likely in a remote region of southeastern Cameroon.[10] The first documented case of HIV dates to 1959 from plasma samples of a patient with sickle cell disease from Kinshasa in the Democratic Republic of Congo.[11,12] The virus likely spread for more than 5 decades prior to its clinical recognition.[13] The first retrospectively documented case of HIV/AIDS in the United States dates back to 1969.[14]

Over the past 39 years, more than 75 million people worldwide have been infected with HIV; at least 32 million of them have died (data on numbers of people in the developing world with HIV are expressed as ranges).[15] Prior to the availability of effective anti-HIV treatment, HIV/AIDS-related mortality grew annually. In 1995, 50,140 people died in the United States from complications related to HIV infection.[16] By 1996, a dramatic advance in the care of HIV-infected patients changed the prognosis and, in time, what it meant to live with HIV infection. The development of highly active antiretroviral treatment (HAART) regimens produced a profound suppression in measurable levels of HIV in the bloodstream. For many individuals, this led to numerical restoration of CD4+ T cells and recovery of immunological competency.[17-19] HAART entailed a strategy to administer a combination of classes of antiretroviral agents that were targeted at different parts of the viral lifecycle. HAART regimens may include non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, protease inhibitors, entry inhibitors, and/or integrase inhibitors.[20] In a single year from 1995 to 1996, HIV/AIDS-related deaths decreased by 23%.[16] Improvements in HIV/AIDS-related mortality continue through today: Between 1987 and 2015, age-adjusted death rates for patients living with AIDS have declined from approximately 375 per 1000 people living with AIDS to fewer than 25.[21] The National Institutes of Health estimate that effective antiretroviral treatment (ART) treatment of HIV has, in the United States alone, saved more than 3 million years of life.[22]

At present, nearly 38 million people worldwide live with HIV/AIDS.[15] As effective anti-HIV treatments have evolved, they have been alternatively called HAART, combination ART, and more recently, simply ART, now the preferred term. Nearly 40 years into the HIV pandemic, despite the broad availability of effective ART, and outside of 2 known individuals who were successfully treated with allogeneic hematopoietic cell transplantation (allo-HCT) that cleared their respective HIV infections, there is still no evidence for a cure for HIV.[23,24]

While effective ART has profoundly reduced the mortality rate and transmission of HIV, and antiretroviral preemptive treatments have provided at-risk individuals with an effective risk reduction tool, the virus continues to take an insidious, inexorable toll upon humanity.[15,25,26] This includes, even in effectively treated individuals, an increased incidence of a number of different cancer types, end-organ injury, and an increased risk of premature death. In addition, lack of access to diagnostic testing and to effective treatment, as well as the impact of numerous social determinants of health, culminate in continued HIV-related mortality. In 2018, 770,000 people worldwide died from complications related to HIV/AIDS.[15]

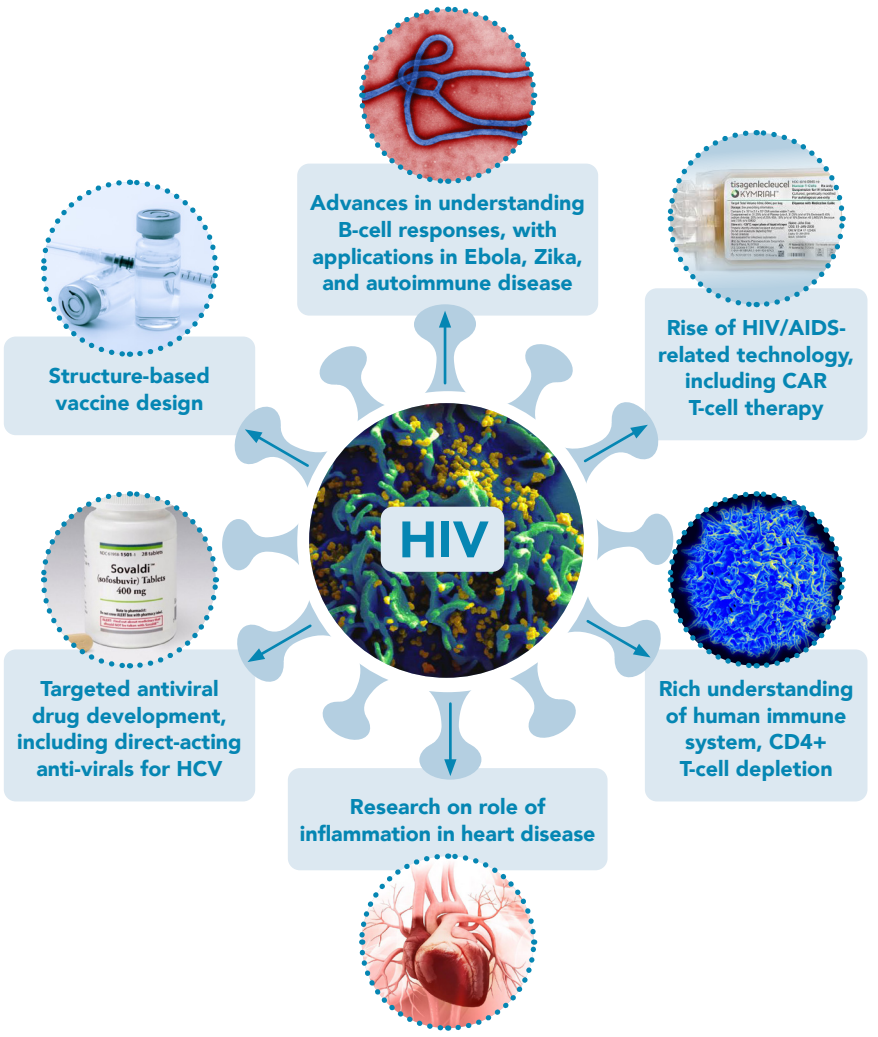
The connections between cancer and HIV/AIDS became clear relatively early in the HIV/AIDS pandemic. Not only were opportunistic infections present in a majority of HIV-infected patients who met the initial diagnostic criteria for AIDS, but several cancer types were far more prevalent as well. These included both cancers that occurred more commonly in severely immunocompromised patients and those that reflected a role for viral coinfection with oncogenic viruses (ie, human herpesvirus-8, human papillomavirus, Epstein-Barr virus, hepatitis B virus). The current diagnostic criteria for stage III HIV infection include invasive cervical cancer, Kaposi sarcoma, and lymphomas (Burkitt, immunoblastic, and primary central nervous system [CNS]) as stigmata of the disease that, in combination with confirmed HIV infection, establish the diagnosis of AIDS.[27]

While there is still much to understand before HIV is fully conquered, we have already learned a great deal about the pathobiology of this virus that has helped advanced immune-oncological technologies and led to the development of increasingly effective gene therapy delivery systems.

Early in the HIV pandemic, prior to the availability of effective anti-HIV treatment, infected patients sometimes presented with relatively unusual lymphoma subtypes, including those typically limited to individuals with severe immunocompromisation (primary CNS lymphoma, primary effusion lymphoma, plasmablastic lymphoma of the oral cavity, and polymorphic B-cell lymphoma).[28] The spectrum of lymphoma types shifted and these relatively rare lymphomas are now less commonly seen. However, patients with effectively treated HIV still remain at an increased risk of non-Hodgkin lymphoma (NHL); the risk has dropped significantly in the post-ART era, but it remains more than 8 times higher than in the non–HIV-infected population.[29] Moreover, HIV-infected patients with lymphoma are still more likely to present with advanced-stage disease, to have involvement at extranodal sites (including a higher risk of central nervous system involvement), and to manifest systemic "B symptoms" at diagnosis.[30,31]

Beyond those malignancies that represent AIDS-confirming diagnoses, population-based data for HIV-infected individuals show that there is a more broadly increased risk for a number of cancer types that are not included as part of the AIDS diagnostic criteria. The Swiss Cohort Study was based on a population-based registry, initiated in 1988, that includes 15,624 patients. The study evaluated not only cancer risk, but additionally provided insights into patterns of transmission, effectiveness of ART, pregnancy outcomes, and patient outcomes.[32] A 2005 review of the registry data confirmed the increased risk of cancer among HIV-infected

FIGURE. Spin-off Effects of HIV/AIDS Research



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Schwetz TA, Fauci AS. The extended impact of human immunodeficiency virus/AIDS research *J Infect Dis*. 2019;1(1):6-9. doi.org/10.1093/infdis/jiy441

individuals. Beyond those increased risks for NHL, cervical cancer, and Kaposi sarcoma that were included in the AIDS diagnostic criteria, these population-based data confirmed an elevated risk for a broader set of cancer diagnoses, including Hodgkin lymphoma; cancers of the aerodigestive tract, anus, liver, and lung; and melanoma and nonmelanoma skin cancers.[33] For cancers of the aerodigestive tract and lung, this increased risk was limited to smokers. The implications of these data are significant in the post-ART era. The authors of the study noted that "HAART treatment may prevent excess risk of [Kaposi sarcoma] and non-Hodgkin lymphoma, but not that of Hodgkin lymphoma or other non–AIDS-defining cancers."[33] Effective cancer prevention for this population therefore includes a risk-adapted screening approach that integrates an awareness of the increased risk of cancer development related to HIV, and it also focuses upon modification of reducible risk factors, like smoking, that may be of enhanced importance for this population.

Prior to the advent of effective anti-HIV treatments, the care of patients with HIV-related lymphomas frequently included dose-attenuated or deescalated regimens that produced poor survival outcomes.[34,35] Following the widespread availability of ART, numerous trials have validated the concept that effectively treated HIV-infected patients may be managed with standard cancer treatment regimens in a manner analogous to those patients without HIV. This approach produces survival outcomes comparable with those of noninfected patients.[36-46] Some evidence indicates that concomitant treatment with effective ART produces better treatment outcomes.[47] Moreover, ART-responsive HIV-infected patients with relapsed, refractory, or persistent blood cancers who otherwise meet transplant inclusion criteria appear to have survival outcomes with autologous HCT and allo-HCT equivalent to those without HIV infection.[48,49] No evidence exists to indicate that therapy with standard treatment has a deleterious effect upon long-term HIV virologic control nor T-cell reconstitution. Patients may, however, develop short-term numerical drops in CD4+ T-cell counts such that they may require prophylaxis against opportunistic infections. When treating this population of patients with standard chemotherapeutic/immunotherapeutic regimens, it is also very important to review the ART regimen carefully, because there is potential for life-threatening drug–drug interactions between these respective regimens.[50]

While enormous progress has been made to date against HIV, complete victory has been elusive. In 2018, 37,832 people were newly diagnosed with HIV infection in the United States. New infections are disproportionately occurring in the southern United States, and African Americans and Latinos now account for a majority of newly diagnosed patients.[51] The 2 individuals who have achieved documented cures of their HIV infection did so through a process that is likely not replicable on a scalable basis. To date, there are still no effective vaccines against HIV.

A key impediment to further progress lies within the unique biology of RNA lentiviruses. Sharp and Hahn note, "HIV-1 evolves around 1 million times faster than mammalian DNA… because the HIV-1 reverse transcriptase is error-prone and the viral generation time is short."[13] This may result in frequent changes to potential antigenic targets, thus limiting the potential effectiveness of candidate vaccines. Moreover, while vaccine-generated neutralizing antibodies may be effective for many viral infections, an antibody response alone may not be adequate to achieve full protection against HIV infection.[52] An effective immune-prophylactic approach to HIV will likely require the generation of a cytotoxic T-lymphocyte response to the virus.[53] In addition, the latent phase of the HIV viral lifecycle may render a significant part of the viral reservoir immunologically invisible, thus reducing the effectiveness of either humoral or cellular immunological responses to HIV. Finally, the complex logistics and economics of vaccine development further complicate the prospects for an effective anti-HIV vaccine.[54]

While there is still much to understand before HIV is fully conquered, we have already learned a great deal about the pathobiology of this virus that has helped advanced immune-oncological technologies and led to the development of increasingly effective gene therapy delivery systems. HIV is a positive-sense RNA lentivirus that efficiently enters CD4+ T-cells; it undergoes reverse transcription to form DNA, which is integrated into host DNA prior to replication, assembly, and subsequent release into the bloodstream.[55] Fortunately, this viral lifecycle can be co-opted for the vector-based gene modification of novel cellular therapeutics or used as a primary delivery system for *in vitro* or *in vivo* therapeutic gene modification.[56] Removal of potential pathogenic genes from the lentivirus can allow for effective Good Manufacturing Practice production of the lentiviral vector, as well as for efficient target cell transfection with neogenes and reproducible clinical activity for the vector.[57] This set of technologies is currently used to produce anticancer chimeric antigen receptor T-cell therapeutics for both commercial and investigational purposes.[58] Lentiviral vectors may also be used as the basis for investigational gene therapy–based treatment for patients with hemoglobinopathies and hemophilia.[59]

EPILOGUE. The AIDS Quilt was conceived in 1985 as a memorial, with each panel representing and documenting a person who lost their life to the HIV/AIDS pandemic. The AIDS Quilt became so large in 2012 that it was moved into a virtual form. At that time, the quilt spanned more than 1.3 million square feet and captured more than 94,000 lives lost to HIV. It is a graphic representation of the scale of devastation and suffering left in the wake of the HIV virus.[60]

With the breadth of resources now available, the prospects for an eventual eradication of human HIV infection seem real—yet still painfully distant. Effective antiviral treatment, earlier diagnosis, behavioral modification, preexposure prophylaxis, and continued advances in vaccine development are the keys to a future without HIV. Advances in HIV treatment, more effective treatments for HIV-infected patients with cancer, and the continued pursuit of further therapeutic innovations for this population of patients portend a future of better cancer care outcomes and more effective cancer prevention. The pain and progress of the past 39 years have led to scientific advances that have implications far beyond the control of HIV infection. As we pause to remember the humanity at the center of all this progress, it is best to look forward with both humility and hope. ◆

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See full reference list online at **AJMC.COM/LINK/4669**.

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