HIV and AIDS
The Unraveling of an Epidemic at ICAAC

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21st ICAAC in Chicago – 1981
Beginning of the HIV epidemic

The presentation was a late addition to an evening session in the large Chicago hotel. Although this was a new problem not yet encountered by most attending ICAAC and there was only one poster at the meeting, the interest was intense and the room was filled to overflow by the time I began my remarks. In my talk, I had predicted a great geographic and numerical expansion of cases and that these cases would not be restricted to a single group or country. We at CDC were often criticized for overestimating and “hyping” the epidemic in the first year or two, but our estimates, in retrospect, were often too low and scope of the problem exceeded the expectations of all.”

–James Curran, then of the US Centers of Disease Control and Prevention, commenting on his overview of the emerging epidemic at the 1981 ICAAC. (CDC)
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IN THE 50 YEARS OF ICAAC, the HIV (human immunodeficiency virus) pandemic stands as the most transformative emerging infectious disease in its history. It began quietly with the initial reporting in the June 5, 1981, issue of Morbidity and Mortality Weekly Reports (CDC, 1981a) of a cluster of five young gay men with Pneumocystis carinii pneumonia (today P. jirovecii pneumonia; PCP) and cytomegalovirus infection at three different hospitals in Los Angeles, California. Soon thereafter, the Centers for Disease Control and Prevention (CDC) described 26 cases of Kaposi sarcoma among gay men (CDC, 1981b). By the end of 1981, 234 deaths in the US were attributed to the new syndrome. From this time on, ICAAC was poised to serve as a major point of encounter for basic, clinical, and public health researchers, as a key meeting for education and information, and eventually as a seed for successful HIV specialty and subspecialty conferences.

Today, with the perspective of time, it is interesting to examine how a large venue such as ICAAC senses the development and spread of an emerging infection in society and informs its participants. It may well be possible, in retrospect, that isolated reports related to consequences of HIV infection had filtered through such venues before the epidemic was formally recognized. However, the official ICAAC HIV clock started beating in the same year, 1981, just a few months after the sentinel MMWR report. A scheduled symposium on emerging diseases (1981, symp. 64) at the 21st ICAAC in Chicago in November of 1981 included the following topics: toxic shock syndrome, Kawasaki disease, and Lyme disease. A special presentation was added to that symposium (not published in the program book) in which James Curran from the CDC described what was currently known about the new syndrome; David Bell recalled that in his presentation Dr Curran cautioned that the syndrome would likely go beyond New York and California and, if infectious, it would spread beyond gay men.

The cover of the June 5, 1981, issue of the Morbidity and Mortality Weekly Report of the US Centers for Disease Control and Prevention. This is recognized as the first published report of the syndrome that would later to be know as AIDS, a consequence of HIV infection.
Early Days of an Epidemic

THOSE WORDS WERE, SADLY, PROVEN TRUE. By 1982, cases were reported all around the US and elsewhere, including in Africa. The CDC formalized the name of the syndrome to AIDS (acquired immune deficiency syndrome) and listed 4 risk groups: homosexual men, recent Haitian migrants, people with hemophilia A, and injection drug users. The 22nd ICAAC in 1982 had a symposium dedicated to *Infectious Diseases in Homosexual Men* (1982, symp. 70), chaired by King Holmes and James Curran, that presented the epidemiologic status of (Harold Jaffe), clinical and immunologic aspects of (Michael Gottlieb), and clinical response to (Frederick Siegal) the syndromes of the immunodeficiency state. In posters and oral presentations, the ICAAC audience was shown many fundamental pieces of the puzzle starting to fit together: the large spectrum of associated opportunistic diseases, the destruction of cellular immunity and shifts in lymphocyte subpopulations that are the crux of current understanding of the immune damage, and the extension of the epidemic to the heterosexual population. Thus, ICAAC described, shortly after the identification of this new epidemic, the importance of the emerging problem, the efforts to build a comprehensive view of the clinical disease, the trends in the epidemic, and the basics of pathogenesis. Still, the culprit, the causal agent, was yet to be described. But not for long.

In 1983, Françoise Barré-Sinoussi and Luc Montagnier at the Pasteur Institute in Paris, and Robert Gallo at the US National Cancer Institute, reported the isolation and characterization of a new human retrovirus (termed lymphadenopathy-associated virus [LAV] and human T-cell lymphotropic virus type III [HTLV-III], respectively), as the causative agent of AIDS.

By then the infection was spreading rapidly, with 33 countries reporting cases. A better understanding of transmission routes led to the first US Public Health Service guidelines for preventing transmission through sexual contact and blood transfusions (CDC, 1983). These guidelines included the exclusion of prospective blood donors based on their being in risk groups known to be associated with HIV/AIDS. Robert Gallo would be invited to present his findings at a symposium dedicated to AIDS at the 23rd ICAAC in 1983. He would share the podium with another rising authority in the field, Anthony Fauci, who would present his work and views on the immune defects of AIDS. By this time, barely 2.5 years since the beginning of the epidemic, ICAAC posted, in addition to the full symposium on AIDS, an oral session dedicated to HIV/AIDS (1983, abst. 219, 221, 222, 223) and 2 dedicated poster sessions (1983, abst. 623, 624, 625, 626, 628, 630, 632A, 953, 962, 963).

At the 1982 ICAAC, this session on infectious disease syndromes in homosexual men focused largely on what would later be called AIDS.
The work presented covered the new and more detailed epidemiologic findings: mother-to-child transmission of HIV; infection in individuals with hemophilia A; disease in populations not previously suspected to be at risk; an enlarging spectrum of disease, including eye and central nervous system manifestations; the mimicry of mycobacterial infection presenting as Whipple disease; and the predictive signs conveyed by oral candidiasis. Lowell Young summarized the principles of management and prevention of infection in people with AIDS in a symposium on the immunosuppressed patient (1983, symp. 92), and numerous posters detailed first-hand experience of the use of trimethoprim-sulfamethoxazole for the treatment of PCP. The growing importance of the field of biomarkers was highlighted by the description of increased levels of beta2-microglobulin (1983, abst. 962, 963), and a by a better understanding of abnormalities in T-lymphocyte subsets (1983, abst. 954).

The isolation of the causal agent of AIDS and its cultivation allowed the identification of host antibodies to HIV—highlighted at several oral presentations at the 24th ICAAC (1984, abst. 62, 63, 64, 65). However, a commercial test was not to be developed and available for routine use until 1985 when the US Food and Drug Administration (FDA) approved the first enzyme-linked immunosorbent assay (ELISA) test kit to screen for antibodies to HIV. Understanding the epidemiology continued to improve, and posters at ICAAC detailed transfusion-associated AIDS (1984, abst. 870), and immunologic dysfunction in drug users (1984, abst. 881). In a symposium dedicated to AIDS (1984, symp. 100), Nathan Clumeck described the worrisome trends of AIDS in Africa, and once again, the audience had the opportunity to be updated on the understanding of the virology and immunology of AIDS through the words of Robert Gallo and Anthony Fauci.

**LAV AND HTLV III** were ultimately found to represent the same virus, which became officially designated as human immunodeficiency virus type 1 (HIV-1) (Coffin, 1986), and the discoveries and developments linked to the isolation of the virus started to bear fruit. The US FDA approved the first commercial HIV antibody test and began screening the blood supply. At the 25th ICAAC in 1985, the CDC and the American Red Cross Blood Service presented their results on the first 10,000 US cases (1985, abst. 223). The 25th ICAAC also conveyed very sensitive information those working or living with HIV-infected individuals. Various studies presented the prospective evaluation and the risk of exposure of health care workers to blood from people with AIDS (1985, abst. 225, 226), and the rates of HIV
Because AIDS symptoms can take up to 10 years to develop, only a small fraction of the epidemic was visible in 1985. The above graphic was shown frequently around this time to demonstrate that AIDS was certain to be the "tip of the iceberg" of this epidemic. 

seropositivity in health care personnel (1985, abst. 224). One study emphasized the lack of household transmission of HIV (1985, abst. 228). Progress in virology allowed studies on viremia in individuals with generalized lymphadenopathy (1985, abst. 220). An additional highly anticipated advance was the development of better therapeutics for the ravaging opportunistic infections associated with HIV infection. In association with several US federal and academic centers (National Cancer Institute, National Institutes of Health, Memorial Sloan–Kettering Cancer Center, Duke University), Wellcome Research Laboratories moved 2 crucial compounds into clinical research: BW A509U (AZT, zidovudine) and BW 759U, 9-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine (DHPG, ganciclovir). Zidovudine was shown to block the reverse transcriptase of HIV-1 (1985, abst. 439), and selectively inhibit HIV infection of T lymphocytes (1985, abst. 440) in culture (1985, abst. 433), and in the feline animal model of AIDS (1985, abst. 438). Ganciclovir, whose intracellular triphosphate inhibits the incorporation of dGTP by the CMV DNA polymerase, was administered to patients for the treatment of the ocular and systemic manifestations of CMV disease (1985, abst. 441, 442, 443). Two abstracts presented the features of aerosol delivery of pentamidine for PCP prophylaxis (1985, abst. 550, 552). Another salient feature of that year was the presentation of the MACS (Multicenter AIDS Cohort Study), a study of 5000 gay men (1985, abst. 740), today one of the pillars of HIV cohort research in the US and worldwide. The growing importance of HIV led to the First International AIDS Conference in Atlanta in 1985, under the auspices of the US Department of Health and Human Services and the World Health Organization.
By 1986, HIV/AIDS had become a central subject at ICAAC. The first scheduled symposium (1986, symp. 1) at the 26th ICAAC, held in the Grand Ballroom of the Hilton Hotel in New Orleans, reflected the growing concern with the epidemic and initiated a tradition for HIV topics opening the annual conferences. New aspects reflecting the diversification of research included discussion of pathogenesis by David Ho, the prospects for a preventive vaccine by Dani Bolognesi, and the progress in treatment by Samuel Broder (1986, symp. 1); and at a separate session, the identification of important genetic variation among HIV isolates by George Shaw (1986, symp. 43).

But, above all, the 26th ICAAC will stay in the memory of many participants because of the electrifying presentation (which was not even included in the official abstract book) of the results from the first, randomized, placebo-controlled clinical trial of zidovudine, a promising first drug for the treatment of HIV infection. The 24-week data showed striking reductions in mortality and progression of HIV disease among the patients in the zidovudine group. Other abstracts illustrated the rush to fully explore the therapeutic possibilities and the toxicity of nucleoside analogue reverse transcriptase inhibitors (nRTIs): for example 3’-azido-2’,3’-dideoxy-5-ethyluridine (1986, abst. 1092) and 9-(1,3-dihydroxy-2-propoxymethyl)-guanine (1986, abst. 1096). The results of the zidovudine trial would be published in two papers by the New England Journal of Medicine in July 1987 (Fischl, 1987; Richman, 1987). A full session was also dedicated to the diagnosis, treatment, and prevention of PCP, including the comparative evaluation of bronchoalveolar lavage versus transbronchial lung biopsy (1986, abst. 686), the early evaluation of monthly pentamidine prophylaxis (1986, abst. 690), and the role of corticosteroids in the management of pneumonia (1986, abst. 692). An analysis comparing the 5 ELISA kits for the diagnosis of HIV infection illustrated the quest for improvement in HIV screening (1986, abst. 1032).

Progress in Drug Development

On March 20, 1987, after only 25 months of evaluation, the FDA approved zidovudine through an accelerated approval system, that being the shortest period to approval in drug development in recent history. The FDA also sanctioned the first human testing of candidate HIV vaccine—still an unfulfilled need in the field today. The organizers of the 27th ICAAC (1987), inserted in the printed program book the following statement concerning the opening session devoted to HIV:

Initial Efficacy of Zidovudine in the Treatment of Patients with AIDS and ARC. The results of the double-blind, placebo-controlled trial of zidovudine (AZT, ZDV) in patients on the later stages of HIV infection (AIDS and AIDS-related complex (ARC)). Presented at the 1986 ICAAC by Margaret Fischl. The results were remarkable: there were 19 deaths in the placebo group and just one death in the drug-treatment groups. Zidovudine was approved by the US Food and Drug Administration for the treatment of AIDS after only about 25 months of evaluation. Research would later show that the clinical benefits of zidovudine alone are short lived; currently, regimens of three drugs provide the most durable benefits available.

(Figure is adapted from Fischl, 1987)
This special HIV session is anticipated to attract an extraordinarily large attendance.

Thomas Quinn, Anthony Fauci, Merle Sande, Martin Hirsch, and Robert Gallo convened at the podium to present the progress in the field and the evidence for a rapidly expanding epidemic. An unprecedented number of presentations and abstracts explored the use of zidovudine, and described new agents, including 2'-3'-dideoxycytidine (ddC, zalcitabine) (1987, abst. 379). The use of polymerase chain reaction (PCR) for the detection of viral RNA was discussed (1987, abst. 592) at this conference—six years ahead of the introduction of a PCR-based commercial test outside of the United States, and eight years before the FDA approved one for use in the US.

On the clinical front, two presentations were of particular interest: the characterization by researchers at the CDC of individuals who were “long-term survivors” (1987, abst. 8), and the alert from areas of high endemicity of tuberculosis of the substantial impact of HIV-associated immunodeficiency (1987, abst. 840) and the cross-linking of these two epidemics.

By 1988, a substantial number of sessions at ICAAC were devoted to HIV/AIDS. Notable features included the search for neutralizing antibodies (1988, abst. 76, 77, 1092, 1093), the understanding of cellular reservoirs—first identified in monocytes and macrophages (1988, abst. 71, 72), and the early experiments with 2',3'-dideoxy-2',3'-didehydrothymidine (stavudine, d4T) (1988, abst. 1301).

Americans with Disabilities Act of 1990 was enacted to prohibit discrimination, including of people with AIDS.

In the ensuing years (1989-1995) there was the long crossing of a desert: increasing numbers of severely sick patients, pressure on the health services, and the ongoing quest for a fully effective...
treatment. The scientific and the clinical research communities improved the diagnostic tools, refined opportunistic infection prophylaxes, and explored new antiretroviral agents. In 1989, Anthony Fauci endorsed the “parallel track” (also called “expanded access”) program for drug access for those who could not qualify for entry into a clinical trial. The 1990 ICAAC devoted a full session to discuss the impact HIV/AIDS was having on training of internal medicine and infectious diseases physicians (1990, symp. 98).

“By 1992, AIDS had become the number one cause of death among US men aged 25 to 44 years.”

Important steps in the management and prevention of HIV infection included the assessment of antiretroviral therapy as prophylaxis in the animal model (1990, abst. 962), its use in the management of occupational exposure (1990, abst. 490), and some years later, the importance of zidovudine to prevent mother-to-child transmission of HIV (1994, abst. 157). But monotherapy presented numerous problems and Douglas Richman described, at the 1991 ICAAC, the potential of combination therapy (1991, symp. 50). His vision would later be confirmed when the modest results observed in the historical Concorde trial of zidovudine monotherapy (Concorde Coordinating Committee, 1994), were to be superseded by the results of the AIDS Clinical Trials Group (ACTG) 175 study (Hammer, 1996) and the European Delta trial (Delta Coordinating Committee, 1996).

In the early 1990s, drugs that were to become pillars of future antiretroviral combination therapy were examined in rapid sequence: lamivudine (3TC), presented at a 1992 symposium by Marc Rubin (1992, symp. 6), as well as the new classes of nonnucleoside reverse transcriptase inhibitors (NNRTIs) (1991, abst. 697, 698, 1337, 1338, 1339), and protease inhibitors (1991, abst. 701). The latter were the result of the new computer-assisted, structure-based drug design, a concept that was presented to the audience by Peter Kollman at a 1991 symposium (1991, symp. 2).

The trial was conceptualized at a French restaurant in Montreal during an International AIDS Congress in 1989 by Tom Merigan, Steve Lagakos, and me. The goal was to compare single-drug therapy (zidovudine) versus two-drug therapy (zidovudine plus didanosine or zalcitabine), based on laboratory studies that we had conducted showing synergistic interactions between two active drugs in vitro. It took the next 2 years to flesh out the protocol (ACTG 175) and convince pharmaceutical companies, the ACTG, regulatory groups, and constituent communities that this trial was worth doing. We also enlisted 3 young investigators at our institutions to lead the study: Scott Hammer (Harvard) and David Katzenstein (Stanford), and the statistician Michael Hughes (Harvard). The study finally opened in December 1991, and within 10 months, 2493 participants enrolled from throughout the United States.”

– Martin Hirsch, referring to the development of the ACTG 175 trial.
Among many extraordinary ICAAC meetings, the 35th meeting in San Francisco in September, 1995, sticks in my mind as a seminal event in the history of HIV/AIDS. This meeting marked the beginning of end of AZT [zidovudine] monotherapy as a treatment for HIV-infected individuals, as data from the landmark clinical trial known as ACTG 175 were first presented there (abstract LB-1).

ACTG 175 was the first large study to demonstrate the superiority of combination antiretroviral therapy over AZT monotherapy, and was soon followed by other important studies such as Delta and CPCRA 007. At the same ICAAC meeting, we saw some of the first detailed presentations of clinical data from trials of HIV protease inhibitors, alone and in combination. These drugs, given in combination with other agents, would soon revolutionize antiretroviral therapy.

Certainly, the 35th ICAAC meeting was a key milestone in the development of what became known as highly active antiretroviral therapy [HAART], which has saved and prolonged the lives of millions of HIV-infected individuals worldwide."

—Anthony Fauci, commenting on landmark data presented at the 35th ICAAC

**THE SCIENCE AND PRACTICE OF CLINICAL TRIALS WAS A CENTRAL ISSUE** by 1992. However, progress on many fronts was limited by growing awareness of the emergence of antiretroviral drug resistance (1991, abst. 628, 644, 1347, 1348, 1350, 1355, 1356), and years later, by the evidence for transmission of resistant viruses (1995, abst. I-276, I-277). Drug resistance was also a growing concern in the treatment and prophylaxis of opportunistic pathogens, such as oropharyngeal candidiasis (1990, abst. 1271). Resistance of *Mycobacterium tuberculosis* (TB) was soon to threaten medical institutions. The public health system witnessed the rapid spread of multidrug resistant (MDR)-TB in inpatient AIDS wards (1991, abst. 3, 249A). The MDR-TB epidemic was a central issue of discussion at the 1992 ICAAC: Michael Iseman presented strategies for dealing with transmission and TB resistance to drugs at the opening symposium otherwise dedicated to HIV.

By 1994, presentations at the ICAAC were providing the early insight into the uses of triple-drug therapy combining two nRTIs and a protease inhibitor (Collier, 1994, abst. I-58) or an NNRTI (1994, abst. I158). The seminal ACTG 175 trial of zidovudine monotherapy versus combination therapy was presented as a late breaker abstract at the 1995 ICAAC; (1995, abst. LB-1, LB-2) reported that “The study is under analysis, significant differences among treatment arms are evident and detailed results will be reported.”


Also in 1996, the IAS-USA published in *JAMA* the first Guidelines for the use of antiretroviral therapy in HIV-infected adults advocating for combination therapy in early HIV using randomized
clinical trial data and extrapolations of basic research (Carpenter, 1996). The importance of triple combination therapy (also called highly active antiretroviral therapy, HAART) was to be the central issue at the XI International AIDS Conference, held in Vancouver, Canada in 1996.

“The basis for our 1996 recommendations was the providential convergence of three watershed series of observations: the demonstration by both the ACTG 175 and Delta-1 trials that dual nRTI therapy was superior to zidovudine monotherapy for initial treatment; the recognition that plasma HIV RNA levels provided a precise means to monitor the effectiveness of therapy; and the indication from early studies that protease inhibitors, when combined with nRTIs, might produce more rapid and profound effect on viral load than nRTIs alone.”

–Charles C. J. Carpenter, then chair of the IAS-USA antiretroviral guidelines panel.

The magnitude of viral replication, with 1 to 10 billion virions produced a day, screamed that the virus should be treated aggressively.”

–Michael Saag, commenting on the implications of data first presented in 1994 on viral dynamics.

A New Era in HIV Treatment

The impact—the revolution—of HAART had a major impact on the nature of presentations and posters at the following ICAAC in Toronto in 1997: dozens of abstracts dealing with the new treatments, mainly around combinations of zidovudine and lamivudine with indinavir, saquinavir, or ritonavir. And these first waves were accompanied by much good news: the decrease in mortality and morbidity (1997, abst. I-17), reductions in hospitalizations (1997, abst. I-182), remission or improvement of intractable infections such as microsporidiosis (1997, abst. I-32) and progressive
multifocal leukoencephalopathy (1997, abst. I-34), and the possibility of discontinuing long-term suppressive treatment for cytomegalovirus retinitis (1997, abst. I-33, I-36) as a result of immune reconstitution.

However, the euphoria was tempered by high rates of treatment failure and drug resistance, and the early indication of toxicity associated with newer treatments: body mass change (1997, abst. I-185), indinavir-associated nephrolithiasis (1997, abst. I-183, I-184), and instances of acute hepatic failure (1997, abst. I-187). New treatments and strategies were already in development for those in whom the initial HAART was failing, as illustrated by a complete session on the use of dual protease inhibitors, generally ritonavir and saquinavir. On another front, but not eclipsed by the treatment success, was the exploration of the new understanding of the CC chemokine receptor 5 (CCR5) delta32 deletion, a host variant of the viral coreceptor that largely protected the homozygous carrier from infection with CCR5-tropic viruses (1997, abst. I-119). Heterozygosity was noted to be associated with slower disease progression in population studies (1997, abst. I-43). Progress in the understanding of viral entry and its potential for therapeutics and microbicides was discussed at the opening session by John Moore (1997, symp. 40-I).

**BY 1998, THE FIELD WAS MATURING,** and many of the key discussions are reminiscent of the issues in today’s HIV medicine: “when to start,” “what to start with,” and “when to switch,” and other aspects that would become more clear with the passage of the time: “salvage therapy” and “when to stop prophylaxis.” The field was also bringing pediatric AIDS to a more prominent position, and accelerating the extension of the benefits of HAART in the adult population to HIV-infected infants and children. Other topics that came to light and to scrutiny were the possibility of using post-exposure prophylaxis (PEP) for high-risk sexual exposures, and the unexpected clinical benefit of the loss of replicative viral fitness associated with extensive drug resistance.

Improvement in understanding the dynamics of HIV viral replication in the mid-1990s had led to the “hit hard, hit early” treatment paradigm. But in the later 1990s, emerging evidence of the difficulty in eradicating HIV infection, the possibility of successful, although partial, immune restoration after advanced HIV infection as a result of treatment, and the recognition of increasing numbers of adverse effects of antiretroviral drugs were moving the pendulum back to later treatment. Two of the pillars of treatment, stavudine and didanosine, were not only increasingly identified as main culprits in lipodystrophy, but also of life-threatening events such as lactic acidosis (1999, abst. I122; I123), and a complete symposium was dedicated to insulin resistance, cardiovascular disease, and lipodystrophy associated with treatment—the latter now
investigated under the light of mitochondrial toxicity (2000, symp. 145). In parallel, a second "emerging epidemic" was identified: the co-infection with HIV and hepatitis C virus (HCV) (1999, abst. H56). In 1999, several groups were presenting their initial experience in the treatment of HCV in coinfected individuals by the combination of interferon alfa and ribavirin (1999, abst. H59; 1999, abst. H60).

**THE 2000 ICAAC WAS REMARKABLE FOR ITS KEYNOTE SESSION** by Beatrice Hahn (2000, abst. 609). By then, evidence of simian immunodeficiency virus (SIV) infection had been reported in 27 different species of African non-human primates, and it was clear that AIDS represented a zoonosis. SIVcpz from chimpanzees and SIVsm from sooty mangabeys, were identified as the immediate precursors of HIV-1 and HIV-2 infection in humans, respectively.

Despite concerns about drug toxicity, and the complexity of the newly coined “salvage” therapy, there was a growing understanding that successful virologic control of HIV-1 infection removed standing contraindications to other interventions that modern medicine had to offer. For example, at the 2001 ICAAC a presentation described “a successful case series” of six patients with HIV with decompensated cirrhosis who received liver transplants (2001, abst. 203). However, there was also growing concern that as people with HIV were living longer, they would be at increased risk for cancer, a forerunner of the concern for non-AIDS events that is now a major area of investigation in the field. A study from the Veterans Administration (2001, abst. 249) indicated that age-adjusted cancer rates were higher among HIV-infected veterans than in the general population.

At the time, the main challenges in the development of new antiretroviral agents included the need to improve potency, develop drugs with diversified resistance profiles, simplify administration (i.e., once-daily dosing), and reduce the potential for toxicity. A 2002 symposium on a new generation of antiretroviral agents (2002, symp. 197) included the presentations of Robert Doms on HIV entry inhibitors (2002, abst. 1782), and of Daria Hazuda on novel integrase strand-transfer inhibitors (2002, abst. 1783). Abstracts and presentations about these compounds dotted the ICAAC program in the following years (e.g., 2003, abst. H-443; 2004, abst. H-1137b; 2005, abst. 1332c). Both lines of research and development would bear fruit, with the approval by the FDA of both maraviroc, a CCR5 coreceptor antagonist, and raltegravir, an integrase strand-transfer inhibitor in 2007.

The early events of HIV infection were also better detailed since the identification by Yvette von Kooyk and collaborators of the role of the dendritic cell (DC)-specific intercellular adhesion molecule 3 (ICAM-3) grabbing integrin (DC-SIGN), a C-type lectin receptor that facilitates

What is now also known, but perhaps less widely appreciated, is that SIVcpz strains have been transmitted to humans on at least 3 independent occasions and that the current HIV-1 group M pandemic, which has afflicted more than 60 million people and caused more than 20 million deaths—resulted from just one of these transmission events in the first half of the 20th century.”

—Beatrice Hahn, commenting on the identification of two simian viruses that were established to be the origins of HIV-1 and HIV-2 in humans, data on which she presented at a plenary session in 2000.
the transmission of HIV to T cells (Geijtenbeek, 2000). She presented progress in that field at the 2002 ICAAC (2002, abst. 1193). The publication of the first draft of the human genome, and technical progress in the large-scale analysis of genetic variation were allowing considerable progress in the understanding of individual predisposition to infectious diseases and of the molecular basis of pathogen-specific responses at the cellular level. The new domain was presented at a dedicated 2002 ICAAC symposium (2002, symp. 64).

**THE FIRST YEARS OF THE NEW MILLENNIUM** had an engaged community that had developed better combination therapies and that was beginning to better understand many of the toxicities associated with the available antiretroviral drugs. More drugs meant more options to contend with in terms of toxic effects as well as viral resistance. A 2004 late breaker presented the results of a trial evaluating the combination of tenofovir, emtricitabine, and efavirenz, a combination that would be in subsequent years used broadly in initial therapy for HIV infection (2004, abst. H-1137c). Resistance was becoming a concern at the population level as transmission of HIV strains with decreased susceptibility to the available drugs was becoming apparent. A presentation in 2004 reported, from a large cohort of antiretroviral-naive subjects from 54 sites in 44 US cities, a prevalence rate of 23% for resistance to 1 or more antiretroviral drugs (2004, abst. H-173). This decreased susceptibility was more common for the NNRTIs than for nRTIs or protease inhibitors. The worldwide epidemiology of primary (i.e., transmitted) HIV resistance was also addressed at a symposium (2004, abst. 1644). Other concerning issues were the implications of low-frequency HIV mutations detected by cloning and sequencing approaches (2004, abst. 1647), and the identification of residual viremia, as a possible mechanism for the emergence of resistance, and as a barrier to eradication of HIV (2004, abst. H-1134).

**Gearing Up for the Long Run**

With the increasing impact of heterosexual transmission of HIV-1, attention was given to the understanding of the basics of mucosal transmission. At a 2004 presentation (2004, abst. 393), Ashley Haase reviewed the mechanisms involved in establishing a persistent infection following...
intravaginal exposure to virus: crossing of the mucosal barrier, the types of cells infected and their role in propagating and spreading infection to the lymphatic tissues.

Myron Cohen in a 2006 symposium (2006, abst. 315d) brought forward a topic that would later become a central point of discussion in the HIV field: antiretroviral drugs as prevention tools. The concept, that almost-universal treatment would decrease transmission of HIV at the population level, has converged with other trends: universal testing and “test and treat” initiatives, as well as additional support for guidelines calling for treatment at higher CD4+ T cell counts (2008, abst. H-896b; Hammer, 2008; Kitahata, 2009). Although the indication for treatment was broadening, the risks of stopping treatment once started (treatment interruption) were being recognized. A presentation at the 2007 ICAAC (2007, abst. H-378) highlighted findings of SMART (Strategies for Management of Antiretroviral Therapy Study Group) (SMART, 2006), a trial that reported an unexpected increase of cardiovascular events after antiretroviral treatment was interrupted. The study underscored the increased immune cell activation and systemic inflammatory responses associated with HIV viremia rebound following treatment discontinuation.

In 2006, the CDC published its new HIV testing recommendations (CDC, 2006), which stated: “The objectives of these recommendations are to increase HIV screening of patients, including pregnant women, in health-care settings; foster earlier detection of HIV infection; identify and counsel persons with unrecognized HIV infection and link them to clinical and prevention services; and further reduce perinatal transmission of HIV in the United States.” Answering this widely perceived call for universal HIV testing, many presentations at the 2008 ICAAC reflected the implementation of those recommendations, in particular at one poster session: opt-out HIV testing in a jail setting, inpatient HIV point-of-care testing, rapid HIV testing in the emergency department, support for increased non-targeted testing, effect of age and race on willingness for rapid HIV testing, accuracy of oral-fluid based HIV tests, and the impact of screening for acute HIV infection. Other issues that reflected shifts in the perception of HIV infection included the emphasis in 2007 on travel precautions and immunization needs of the healthy HIV-infected population (2007, abst. 2025b), reflecting the increased mobility of HIV-infected individuals for tourism and business travel.

The life cycle of HIV-L. At left, the virion is shown attaching to the CD4+ receptor and chemokine coreceptor and subsequently entering the host CD4 cell. Inside the cell, transcription of HIV RNA to HIV DNA is catalyzed by the HIV reverse transcriptase enzyme. The HIV DNA then forms a double-stranded DNA (dsDNA) complex, enters the host cell nucleus and integrates with the host genetic material via the HIV integrase enzyme. Upon activation, the viral DNA is transcribed into viral messenger RNA (mRNA) that in turn is translated into viral precursor proteins. The new HIV RNA and viral precursor proteins are assembled and the virus buds and is released from the cell surface. After budding, viral precursor proteins undergo processing by the HIV protease enzyme and form a mature, infectious viral particle. [Reprinted with permission from Topics in HIV Medicine ®]
ON THE BASIC SCIENCE AND PATHOGENESIS FRONTS, several issues were capturing great attention in 2007. The absence of SIV-associated pathogenesis in several naturally infected hosts, most prominently the sooty mangabeys, was presented by Guido Silvestri at a symposium on HIV pathogenesis (2007, abst. 643). In contrast to HIV infection in humans and experimental SIV infection in Asian macaques, natural SIV infection in African non-human primates is asymptomatic despite high levels of virus replication. These models are remarkable by the absence of generalized immune activation. Elucidation of the pathways by which the differences in immune activation between natural and non-natural hosts are manifest holds promise for the design of novel therapeutic approaches to HIV infection. George Shaw presented at the 2008 joint ICAAC-Infectious Diseases Society of America (IDSA) meeting the latest in our understanding of the nature of the transmitted virus (2008, abst. 3686). By identifying the characteristics of the virus that is acquired during primary infection and its subsequent fate, researchers have been able to confirm the low number of unique strains involved in a successful transmission event and the rapid divergence and adaptation to the new host. This includes the capacity to characterize the innate and acquired immunity forces that play a role as barrier to viral spread. The immune control and immune failure in HIV infection was discussed at an IDSA award lecture given by Bruce Walker (2008, abst. 3649).

The global nature of the HIV epidemic—the global nature of modern epidemics—was the subject of the 2008 Keynote lectures by Anthony Fauci and Kevin De Cock (2008, abst. 830, 830a). That year, the Nobel Prize in Physiology or Medicine in 2008 recognized the discovery of the AIDS virus. The 2009 ICAAC was honored by an address by the Nobel laureate Françoise Barré-Sinoussi, where she described the hurdles in vaccine development. Inevitably, the eyes turned once more toward HIV latency, labeled as “the last frontier” by Douglas Richman at the 2009 pathogenesis symposium (2009, abst. 482; Richman, 2009).

TODAY, ALMOST THREE DECADES SINCE THE BEGINNING OF THE EPIDEMIC, the medical and scientific community can claim many successes in the fight against HIV/AIDS. ICAAC should be recognized as an encounter point where many of the difficulties and doubts in the field were debated, and the place were many milestones in HIV research and care were reached. The most recent keynote symposia and oral presentations and the strong support provided by hundreds of abstracts, are once more setting the agenda and the goals for the coming years.

For five decades, the ICAAC has been a fantastic place of information and exchanges between generations of health professionals and scientists, stimulating worldwide multidisciplinary collaborations. These conferences have been and will remain an invaluable event to globally mobilize clinicians and researchers in response to emerging infectious diseases like HIV/AIDS.”

--Françoise Barré-Sinoussi, corecipient of the Nobel Prize in Physiology or Medicine 2008 (© Institute Pasteur)