



DEAR READER

This is a very special issue of *RITA!* The publication has been produced since 1995, as the first program of The Center for AIDS: Hope and Remembrance Project (CFA). Since then, the publication has evolved from a treatment and research newsletter to a literature-review and HIV advocacy journal indexed by the National Library of Medicine in *PubMed* and subscribed to by thousands of individuals across the US and internationally. It is accessed online tens of thousands of times each year. Perhaps most importantly, it is still offered free of charge, thanks to the generous funders listed on the inside cover.

But *Research Initiative/Treatment Action!* is more than a publication. In many ways, it represents what The CFA is all about. In fact, people still call or e-mail us asking if “Rita” is available to answer some questions (probably because of the publication’s e-mail address: rita@centerforaids.org)! *RITA!* is an essential component of The CFA’s unique information, education, and advocacy work. It is an information medium, a sounding board and voice for advocacy, and a record of our epidemic.

This issue of *RITA!* reviews the past 10 years of highly active antiretroviral therapy (HAART). In some ways, it is also a “year book” for The CFA, reflecting on the 10-year history of the organization, which was founded to combat a dearth of vital information, as well as an abundance of misconceptions and confusion, when new treatments started to become available to treat HIV/AIDS. In 2005, The CFA has been renamed as The Center for AIDS Information & Advocacy. The organization has a renewed mission and purpose to “empower people living with HIV to make informed decisions about their healthcare by providing the latest research and treatment information and by advocating for accessible, affordable, and effective treatment options until there’s a cure.” A decade of service and meeting new challenges in this epidemic has proven that we are in this for the long haul.

When Joel Martinez, my friend and mentor, hired me as editor at The CFA in the year 2000, I began a journey of personal and professional growth that centered on the premise that this epidemic must be conquered. We are on our way there, but (contrary to popular sentiment in the US) have not yet arrived. HAART has been an important stepping stone, but for the many reasons discussed in this issue, it is neither economically nor medically a long-term solution to the global pandemic. We must do better, and with commitment and vigilance, we shall.

RITA! was Joel’s “baby,” his dream. That dream did not die with Joel in November 2003. Rather it continues as strong as ever, with his memory driving The CFA forward. This issue of *RITA!* is dedicated to Joel. We know that HIV is still taking away our loved ones. We also know this disease is unlike any other because of stigma and marginalization, because of ignorance, and because of poverty. Times have certainly changed in HIV/AIDS since 1995, but the disease marches on, and so must we—until there’s a cure.



Very truly yours,
The Center for AIDS Information & Advocacy

Thomas Gegeny, MS, ELS
Senior Editor

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CFA Community Impact Assessment: Summary

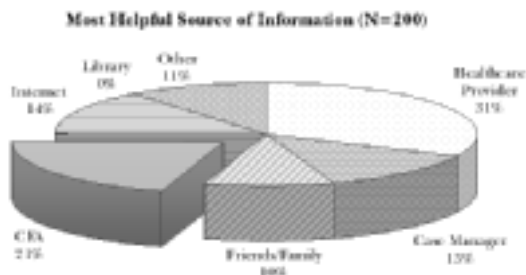
At the request of The Center for AIDS Information & Advocacy (The CFA), the Office of Community Projects at the Graduate School of Social Work, University of Houston conducted a study to document the impact of The CFA during its first 10 years. Key informant interviews ($n=19$) and a community survey ($n=268$) were used to answer 3 research questions.

1. What do constituents value about The CFA?

Across all constituent groups, The CFA is valued as the provider of current, reliable, and useful information. In addition to the quality of the information available, constituents value the way the information is delivered. Many value the efficiency of the Web-based publications and weekly e-mail newsletter. Constituents, particularly people living with HIV/AIDS, appreciated the respectful, empathic, and empowering way CFA staff deliver information in formal classes, as well as individual consultations.

The CFA was seen as having 2 qualities that make it a valuable advocacy partner: understanding of the sciences of HIV pathology and treatment, as well as knowledge of the community.

Funders and the volunteer leadership appreciate 3 organizational characteristics: the unique focus, its structure as a learning organization that uses creativity and analytical thinking to improve services, and the organization's ability to balance quality and expanded services with efficiency.



2. How has The CFA influenced treatment decisions or practice?

In the survey of 268 persons drawn from across Houston, 33% reported turning to The CFA for information when making treatment decisions. Of the 220 persons who indicated a single source of information as most helpful, 21% so identified The CFA. Forty-four percent of respondents had used

CFA services and programs. Data from the key informant interviews suggest that The CFA's impact goes beyond supporting treatment decisions, to empowering people through knowledge and thus enabling them to take control of their lives and to work in their communities to help others.

The impact of The CFA's advocacy on treatment access is less amenable to measurement. The results of advocacy are often incremental and attributable to a team effort. However, based on the key informant interviews, it is clear that The CFA is seen as a valued partner that brings the needs of the HIV affected community to the attention of researchers and other decision-makers through participation in advisory boards, work groups, and national conferences.

3. What do constituents want/need from The CFA?

Fourteen of the 19 key informants recommended that The CFA work to raise awareness of its services among those living with HIV/AIDS, as well as the general medical community. Populations of special concern were young people, the newly diagnosed, ethnic/racial minorities, and women.

Respondents encouraged The CFA to expand its advocacy efforts in 2 ways. First, respondents noted that given continued budget cuts in HIV/AIDS services, The CFA needs to expand the range of its efforts from advocacy for access to clinical trials and new treatments to advocacy for access to quality treatments. Secondly, respondents would like The CFA to take an active role in advocating for vaccine development.

In summary, from the perspective of its constituents, The CFA has carried out its mission of information and advocacy effectively.

The full report will be posted on The CFA website: centerforaids.org. This survey was made possible with support from Swalm Foundation.



HAART at 10 - A CFA timeline

Please note: the events and trends listed on this timeline are by year only and are not listed in any particular order within each year. The sources of information used for this timeline include CFA publications, public record, peer-reviewed literature and conference proceedings, and Internet-based timelines from AEGiS (aegis.org), Kaiser Family Foundation (kff.org), and Gay Men's Health Crisis (gmhc.org). Not all events, deaths, or data could be included in this timeline.

1995

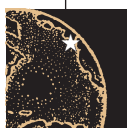


■ The FDA approves the nucleoside reverse transcriptase inhibitor (NRTI), lamivudine (EpiVir, 3TC), by accelerated approval.

■ December 6, 1995: the FDA approves saquinavir (Invirase) in a record 97 days. This is the first antiretroviral drug in the protease inhibitor (PI) class indicated for the treatment of HIV disease. This is essentially the beginning of HAART—Highly Active Anti-Retroviral Therapy.

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■ The FDA approves the chemotherapy agent doxorubicin liposome injection (Doxil) for the treatment of Kaposi's sarcoma (KS) in patients with AIDS whose disease has progressed on prior chemotherapy or in patients who cannot tolerate these other chemotherapy agents.



■ The US Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA) publishes the *USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with HIV* on July 14, 1995.

■ 2nd National Conference on Human Retroviruses and Related Infections is held in Washington, DC.

■ US acknowledges role played by the Institut Pasteur (France) in co-discovering HIV as the virus that causes AIDS.

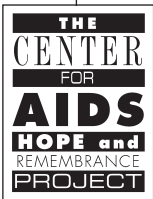


■ Founding of the International Association of Physicians in AIDS Care (IAPAC).

1995



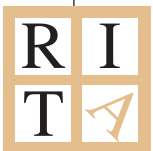
■ The Centers for Disease Control (CDC) announces that AIDS has become the leading cause of death for Americans aged 25 to 44. The biggest increase is reported among men of color who have sex with men.



■ President Clinton establishes Presidential Advisory Council on HIV/AIDS. The First White House Conference on HIV/AIDS is held.

■ In 1995, the CDC reports new cases of AIDS reach 74,180 in the US and the cumulative total number of AIDS cases in the US is 513,486. However, tracking of HIV infections is still not widely instituted.

■ Founding of The Center for AIDS: Hope & Remembrance Project (CFA), a dba of AIDS Research Consortium of Houston.



■ The *RITA! Fax Newsletter* (later renamed in 2000 as the *RITA! Weekly Newsletter*) is launched as a convenient information product for receiving weekly news on HIV treatment and research (more information: centerforaids.org/rita/weekly.htm).



■ First issue of *Research Initiative/Treatment Action! (RITA!)* is published and includes coverage of a paper published on March 3 in *The New England Journal of Medicine*: the use of interleukin-2 (IL-2) in 10 patients with HIV. Six patients experienced increases in CD4 counts.



■ AIDS patient receives baboon bone marrow cells in an effort to boost his immune system, a strategy that ultimately did not prove successful.

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1996

■ US Congress reauthorizes the Ryan White CARE Act.



■ The FDA approves the PIs ritonavir (Norvir) and indinavir (Crixivan).

■ The FDA approves nevirapine (Viramune). This is the first anti-HIV drug in the class called non-nucleoside reverse transcriptase inhibitor (NNRTI).



■ The Levine Committee calls for an overhaul of AIDS research at the National Institutes of Health (NIH), including a stronger role for the Office of AIDS Research (OAR) and increased support for vaccine-related and investigator-initiated research.

APPROVED



■ The FDA approves the viral load test, a new diagnostic test that measures the level of HIV in the blood.



■ International AIDS Vaccine Initiative (IAVI) forms to speed the search for an effective HIV vaccine.

■ Brazil begins a national distribution of anti-retrovirals. They are the first developing country to do this.



■ The Joint United Nations Program on HIV/AIDS (UNAIDS) begins operations; it is established to advocate for global action on the epidemic, and to coordinate HIV/AIDS efforts across the UN system.

■ “Hit hard, hit early” theory of HAART initiation is popular.



■ HIV is no longer the leading cause of death for all Americans ages 25 to 44, but remains the leading cause of death for African Americans in this age group. Also, the number of new AIDS cases diagnosed in the US declines for first time in the history of the epidemic, though incidence varies by sex, race, and ethnicity.

■ Cover stories hailing AIDS breakthroughs and the “end” of the epidemic appear in *The New York Times Magazine*, *The Wall Street Journal*, and *Newsweek*.

1996

■ Using a mathematical model, David Ho and colleagues estimate that HIV infection might be eradicated in approximately 3 years using HAART. This model was later shown to be wrong.



■ *RITA!* and other publications begin discussing the development of virus resistant to HIV drugs, an obvious issue overshadowing the hope provided by HAART.



■ Researchers show KS is caused by a herpes virus (Human Herpesvirus-8 or HHV-8).

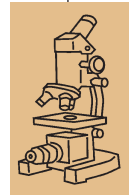


■ Data presented at *3rd International Congress on Drug Therapy in HIV Infection* focuses on positive effects of IL-2.

■ Chemokine receptors CCR5 and CXCR4 are identified as the main co-receptors for HIV.



■ AIDS researcher, David Ho, is *TIME* magazine's 1996 Man of the Year.



■ Interest grows in HIV-positive patients whose disease does not progress to AIDS. Tony Fauci and colleagues publish an important paper in *Science*.



■ The *11th International AIDS Conference* ("One World, One Hope") in Vancouver, Canada highlights the effectiveness of HAART, creating period of optimism. At the conference, David Ho asserts that antiretroviral therapy might cure HIV infection.

■ Abbott and Roche initiate studies that will examine the effect of combining ritonavir and saquinavir. Data are presented at *36th Interscience Conference on Antimicrobial Agents and Chemotherapy* (ICAAC).

■ *3rd National Conference on Human Retroviruses and Related Infections* is held in Washington, DC.



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1997



■ The FDA approves the NNRTI delavirdine (Rescriptor).

■ The FDA approves new formulation of saquinavir (Fortovase, a soft-gel formulation designed to improve absorption in the body).



■ US Congress enacts FDA Modernization Act of 1997, codifying accelerated approval process, and allowing dissemination of information about off-label uses of drugs.

■ The FDA approves Combivir, a combination of zidovudine (Retrovir, AZT) and lamivudine (Epivir, 3TC).

■ CDC reports annual AIDS deaths dropped in the US. In fact, AIDS-related deaths in the US decline by more than 40% compared to the prior year, largely because of HAART.

■ The FDA approves the PI nelfinavir (Viracept).



■ Interest in treating HIV-positive patients during primary HIV infection grows as several cohorts are studied. A study in *Science* by Bruce Walker's group reports strong HIV-1-specific proliferative responses following treatment in acutely infected patients.



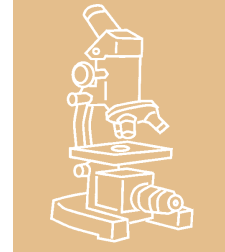
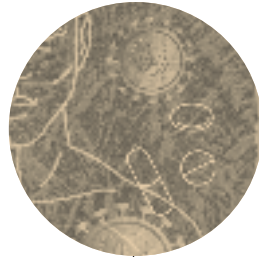
■ Case reports of "Crix Belly," "Buffalo Hump," and "Protease Paunch" are becoming widespread—early signs of what would generally become known as the "lipodystrophy" syndrome, a complex cluster of metabolic and morphologic changes seen in HIV-positive patients, usually while taking HAART.

■ President Clinton announces goal of finding an effective vaccine in 10 years and the creation of Dale and Betty Bumpers Vaccine Research Center.

■ Studies in *Science* and other journals report that HAART fails to clear all virus from the body, even when therapy is started soon after infection.

1997

■ The Oncologic Drugs Advisory Committee (ODAC) recommends FDA approval of paclitaxel (Taxol) as second-line treatment for KS.



■ RITA! and other publications begin exploring new genotypic and phenotypic assays in development as potential ways to manage HIV drug resistance. However, many clinicians are not really sure what to do with this new information or how to interpret it, an issue that still rings true today.

■ ACTG 320 shows “induction/maintenance” (strategy of induction with triple-drug therapy and later maintenance with dual NRTI therapy to control infection) does not work.

■ Drug resistance continues to be a hot topic for clinicians and researchers alike, as the “treatment-experienced” patient population becomes better characterized through “treatment failure.”

R I
T A



■ The 1st National AIDS Malignancy Conference is held at the NIH in Bethesda.



■ The renamed 4th Conference on Retroviruses and Opportunistic Infections (CROI) is held in Washington, DC.

- 37th ICAAC highlights:
- “Hit hard, hit early” paradigm questioned as best management strategy
 - Emerging data on HIV/HCV co-infection
 - Study of Videx (didanosine, ddI) and hydroxyurea shows decreased viral load in patients with HIV
 - Dual PI treatment strategy (including ritonavir as one PI) discussed by John Mellors: a prelude to the future role of boosted PIs as a virtual standard of care

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1998

■ Treatment Action Campaign (TAC) forms in South Africa as a grassroots movement pushing for access to treatment.



■ African Americans account for 49% of AIDS deaths in the US. Mortality for African Americans is almost 10 times that of whites and 3 times that of Hispanics.



■ The US Supreme Court in *Bragdon v. Abbot* rules that the Americans with Disabilities Act covers those in earlier stages of HIV disease, not just AIDS.

■ The FDA approves the NNRTI efavirenz (Sustiva).

■ African-American leaders declare an HIV/AIDS “state of emergency” in US.

■ The FDA approves the NRTI abacavir (Ziagen).

■ The CFA, together with the Bering Community Service Foundation and Treatment Action Group in New York, hosts the first *Houston Treatment Advocacy Forum*.



■ Despite optimism about HAART and apparent decreased incidence of and mortality from opportunistic infections (OIs), several reports indicate growing signs of treatment failure and side effects.

■ Roy Gulick and a multicenter team report the longest patient follow-up to date showing that the simultaneous initiation of indinavir (Crixivan), zidovudine (Retrovir, AZT), and lamivudine (Epivir, 3TC) therapy is superior to sequential initiation (*JAMA*).



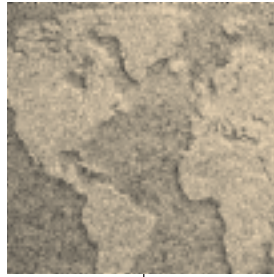
■ AIDS groups protest DuPont’s pricing of efavirenz (Sustiva) by dumping empty pill bottles from a black coffin. Members of ACT-UP storm DuPont’s New York offices demanding the company cut the price of efavirenz. The CFA takes a controversial public stance supporting DuPont’s pricing of efavirenz in the name of HIV research and development.

■ April 24, 1998: Because of the rapid advances in the field of HIV research (primarily the development of antiretroviral therapy and measurement of viral load) there is a paradigm shift in the way HIV is treated, in contrast to previous guidelines, which focused on preventing and treating OIs. The US Department of Health and Human Services (DHHS) and CDC issue *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents* and the *Report of the NIH Panel to Define Principles of Therapy of HIV Infection*.

1998

■ June 17, 1998: US guidelines recommend that treatment be offered to patients with acute syndrome, those within 6 months of seroconversion, and patients with symptomatic disease. For asymptomatic HIV-positive patients, the guidelines recommend treating individuals with fewer than 500 CD4 T cells or plasma HIV RNA (viral load) levels over 20,000 copies/mL (using the RT-PCR assay).

■ Bruce Walker's group at Massachusetts General Hospital takes one HIV-positive patient off HAART to see if his immune system will be able to actively control his infection. The volunteer had been receiving HIV medications for about a year and a half and began treatment almost immediately after infection. This case study introduces the theory that initiating HAART during primary (acute) HIV infection (or PHI) can alter the immune system's ability to control HIV in the long term. This represents one of the earliest attempts to study "structured treatment interruptions" during PHI.



■ Several studies from around the world show induction/maintenance strategy is not feasible using currently available antiretroviral agents.

■ A paper in *The New England Journal of Medicine* reports that zidovudine (Retrovir) reduces rates of perinatal transmission, even when used as an abbreviated regimen that is begun intrapartum or in the first 48 hours of life. Previous recommendations included a 3-part regimen over many weeks, which is not always possible.



■ Reports of cardiovascular problems in patients being treated with PIs begin to appear in the literature.

■ Several researchers report body changes that appear to be related to new combination drug therapies, particularly those that include a PI. Letters to the editor of the *The Lancet* discuss abnormal fat distribution in HIV-positive patients on PI therapy. A report in *AIDS* by Andrew Carr and colleagues describes the physical and biochemical changes occurring in HIV-positive patients taking PIs, defining lipodystrophy syndrome for the first time.

■ The 5th CROI is held in Chicago. The strategy of "hit hard, hit early" continues to be questioned. The opening address discusses lymph nodes as main reservoirs of HIV after HAART.

■ Interest in drug resistance increases as treatment failures grow and transmission of resistant virus is documented in the *Journal of Virology*, *The New England Journal of Medicine*, and other journals.

■ VaxGen Inc. wins federal support for a 3-year AIDS vaccine study (AIDS/Vax) involving 7,500 healthy human volunteers. This is the first large-scale human trial and first phase III trial to determine the efficacy of the gp120-based vaccine.

■ The 12th International AIDS Conference ("Bridging the Gap") is held in Geneva, Switzerland.

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1999



■ Multicenter AIDS Cohort Study (MACS) reaches 15-year mark.

■ Studies begin to see increased rash in women versus men using nevirapine (Viramune).

■ The FDA approves the PI amprenavir (Agenerase).



■ Multiple groups report continued viral replication even in patients with “undetectable” viral loads, suggesting that viral reservoirs persist even in the presence of suppressive therapy. Eradication of HIV with current medications is deemed unlikely.

■ The FDA approves a supplement to the Amplacor HIV-1 Monitor Test, extending the lower limit of viral load quantification from 400 to 50 copies/mL.

■ Studies suggest that many newly infected HIV-positive individuals are carrying forms of the virus that are already resistant to some antiretrovirals (20% to 30%).

■ ViroLogic, Inc. announces the commercial availability of PhenoSense, the company’s rapid phenotypic HIV drug resistance assay.

■ AIDS becomes the world’s deadliest infectious disease in the last year, overtaking tuberculosis and moving up to 4th place among all causes of death worldwide, according to WHO.

■ Bristol-Myers Squibb sends a warning letter to healthcare providers regarding pancreatitis with the NRTI didanosine (Videx, ddI).



■ Debate continues regarding the use of therapeutic drug monitoring, which has since been adopted as standard of care in some European countries, but not in the US.

■ In an article published in *The Lancet*, doctors in Scotland warn against a possible interaction between sildenafil (Viagra) and PIs.

■ Resistance testing (genotypic and phenotypic) is evaluated as a potential tool for clinical management of patients.

■ Studies continue to report increased incidence of heart attack in patients taking HAART.

■ Researchers, particularly in the United Kingdom and Europe, emphasize that there may not be a need to initiate treatment until CD4 counts approach 200.

■ Reports surface of lipodystrophy in HIV-positive patients not taking PIs.

■ *The Wall Street Journal* and *The New York Times Magazine* publish articles on the “Berlin Patient.” As reported at the 6th CROI, this patient showed no evidence of virologic rebound during the 551 days following permanent discontinuation of HIV therapy. HIV was still detected in the patient’s lymph nodes and in resting CD4 T cells but at a low frequency.

■ Interest and research into structured treatment interruptions (also known as strategic treatment interruptions or STIs) in the non-PHI setting explodes as the theory of “autovaccination” becomes very popular. Such therapy interruptions, researchers speculate, might act as a vaccine.

■ A monumental study (HIVNET 012) is conducted in Uganda with results published in *The Lancet*. The study finds that a single dose of nevirapine (Viramune) taken orally by the mother while in labor, followed by a dose for the baby 3 days after birth, reduces the HIV transmission rate by half compared to a similar short course of zidovudine (Retrovir, AZT). This is an important move to simplify regimens to reduce mother-to-child transmission in resource-poor settings. (In 2004, questions will arise about the ethics of this trial with regard to the development of drug resistance, deaths caused by adverse reactions, etc.)

■ The 6th CROI is held in Chicago. Several groups investigate the addition of IL-2 to a HAART regimen. Researchers from the National Institutes of Allergy and Infectious Diseases (NIAID) report that patients receiving IL-2 and HAART have much lower levels of resting CD4 T cells carrying replication-competent HIV than patients receiving HAART alone. However, a study in *The Lancet* reports that HIV activity continues in patients with successful viral suppression whether or not they received IL-2.



1999

■ Hope for STIs hinges on the observations from scientists at Massachusetts General Hospital that while HIV comes back each time the drugs are halted, there are signs the patients’ immune systems are fighting to control the virus, with growing success.



■ The International Perinatal HIV Group publishes a meta-analysis of 15 prospective cohort studies in *The New England Journal of Medicine* showing that elective Caesarean section cuts the risk of HIV transmission in half.

■ 1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV is held in San Diego. At the workshop, a theory gains attention that mitochondrial dysfunction may be a component of lipodystrophy syndrome, specifically mitochondrial toxicity caused by NRTIs.

■ May 1999: Meeting titled *The Challenges of Clinical Trial Design in Assessing the Effects of Anti-HIV Therapy in Heavily Pre-treated Patients* is held in Toronto, Canada. (The CFA cosponsors a follow-up meeting, *The Salvage Therapy Think Tank*, in April 2004.)

■ Two major studies investigate the effect of IL-2: ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial) and SILCAAT (Subcutaneous IL-2 in HIV-infected Patients with Low CD4 Counts under Active Antiretroviral Therapy). ESPRIT investigators will accrue 4,000 patients and randomize them 1:1 to antiviral therapy plus or minus IL-2 and follow them for at least 4 years. SILCAAT is a 4-year trial in which researchers will randomize 1400 subjects with CD4 counts between 50 cells and 300 cells to IL-2 plus antiviral therapy or antiviral therapy alone. Chiron Corporation is the maker of Proleukin brand IL-2 and the study sponsor for SILCAAT. The NIH is sponsoring ESPRIT.

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2000

■ The FDA approves Kaletra, a combination pill containing 2 PIs, lopinavir and ritonavir (Norvir), where a small dose of ritonavir is included to boost levels of lopinavir.

■ The FDA approves Glaxo Wellcome's application to market Trizivir. Trizivir combines the NRTIs zidovudine (Retrovir), lamivudine (EpiVir), and abacavir (Ziagen) into one tablet.

■ President Clinton announces the Millennium Vaccine Initiative, creating incentives for the development and distribution of vaccines against HIV, tuberculosis, and malaria.

■ US and UN Security Councils declare HIV/AIDS an international security threat.

■ South African president, Thabo Mbeki, embraces the denialist theory that HIV does not cause AIDS, thereby hindering efforts to treat HIV-positive patients in his country.



■ The FDA approves a film-coated nelfinavir (Viracept) tablet (for ease of administration).

■ CDC reports that, among men who have sex with men in the US, African-American and Latino cases of HIV exceed those among whites.

■ The FDA approves Bristol-Myers Squibb's enteric-coated didanosine (Videx EC) capsules.

■ Kiyoshi Kuromiya, founder of Critical Path AIDS Project, dies on May 9, 2000.



■ UNAIDS, WHO, and other global health groups announce joint initiative with 5 major pharmaceutical manufacturers to negotiate reduced prices for AIDS drugs in developing countries.

■ The 7th CROI is held in San Francisco.

■ Attention grows regarding co-infection with hepatitis C virus (HCV) as a major co-morbidity in HIV-positive patients.

■ US Congress reauthorizes the Ryan White CARE Act for the second time.

■ CDC statistics: The estimated number of AIDS cases diagnosed in 2000 in the US is 41,267. The estimated number of people living with AIDS in the US is 334,731. The estimated number of deaths of persons with AIDS in the US in 2000 is 17,741. Cumulative deaths from AIDS since the start of the epidemic number 459,518 people.

■ In May 2000, a panel of the International AIDS Society–USA (IAS–USA) endorses the use of drug resistance testing.

■ September 2000: Bruce Walker’s group publishes a paper in *Nature* about initiating HAART in patients with PHI. The researchers conclude that there may be a benefit to this strategy after patients were able to maintain a degree of viral control (5 out of 8 subjects remained off therapy with viral loads of less than 500 copies/mL after a median 6.5 months of stopping HAART). Measures of virus-specific immune function in these patients were also increased.

2000

■ Warning is issued about potentially fatal hepatotoxicity seen with nevirapine (Viramune). Patients taking nevirapine should be monitored carefully during the first 12 weeks of nevirapine therapy.

■ Interactions become apparent between PIs and certain statins, a class of drugs increasingly used to treat hyperlipidemia as a result of HAART. A degenerative muscle condition called rhabdomyolysis can result from this drug interaction.

■ HAART and cancer: While incidence of KS dramatically decreases in the era of HAART, other cancers persist, illustrating new health challenges faced by people living with HIV in the HAART era.

- Incidence of KS and primary brain lymphoma in people living with HIV/AIDS has declined, but trends are less certain for cervical, anal, and lung cancers as some research indicates the incidences of those cancers may have increased.
- According to a 2000 study conducted by the International Collaboration on HIV and Cancer, incidence of KS and non-Hodgkin’s lymphoma (NHL) are lower in the era of HAART. Rates of other cancers seem unchanged.

■ The first CFA *Basic Science Workshop* is held on October 12, 2000.

■ Entry inhibitors gain attention as a potential new class of antiretrovirals.



■ November 1, 2000: *The New York Times* reports that the Immune Response Corporation “tried to block the publication of a scientific paper that showed its HIV vaccine “Remune” was not effective (ie, did not have a dramatic effect on disease progression), and it has asked for damages of more than \$7 million from the universities and researchers who published the findings.” The disputed paper is published in the same day’s issue of *JAMA*. Remune was originally developed by Dr. Jonas Salk more than 10 years earlier as a possible therapeutic vaccine.

■ 13th International AIDS Conference (“Breaking the Silence”) is held in Durban, South Africa. This is the first International AIDS Conference to be held in a developing nation and heightens awareness of the global pandemic.



■ A paper published by Daniel Kuritzkes and colleagues in the *Journal of Acquired Immune Deficiency Syndromes* contributes to the body of evidence showing that dual NRTI therapy, although able to suppress virus for some patients for a limited duration, is not as strong as triple combination therapy in terms of keeping resistance at bay for the longest duration. Most of the remaining interest in dual NRTIs as suppressive therapy for HIV has waned by this point in the HAART era.

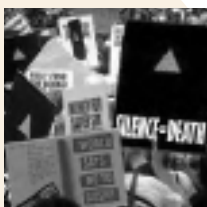
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2001

■ The FDA approves tenofovir (Viread). This drug is a nucleotide reverse transcriptase inhibitor, similar in action to the NRTI class of HIV drugs.

■ AIDS organizations mark the 20th anniversary of the AIDS epidemic in the US in June.



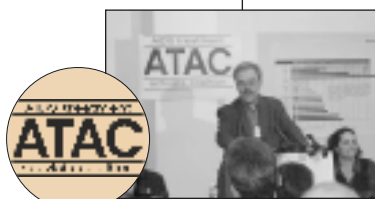
■ February 5, 2001: US guidelines are updated and now recommend delaying therapy in asymptomatic HIV-positive patients until CD4 T cells are less than 350 or viral load is greater than 55,000 copies/mL (with RT-PCR).

■ The FDA approves the first genetic test designed to look at virus mutations in an HIV-infected person. The test is called "TruGene."

■ Generic drug manufacturers offer to produce discounted, generic forms of HIV/AIDS drugs; several major pharmaceutical manufacturers agree to offer further reduced drug prices in developing countries.

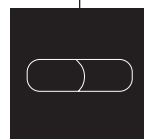
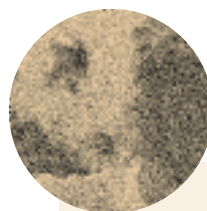
■ HIV/AIDS has the distinction of being a leading cause of human death worldwide.

■ The World Trade Organization, meeting in Doha, Qatar, announces the "DOHA Agreement" to allow developing countries to buy or manufacture generic medications to meet public health crises, such as HIV/AIDS.



■ AIDS Treatment Activists Coalition (ATAC) is founded in August 2001 at a meeting in Houston hosted by The CFA (atac-usa.org).

■ The CFA's patient newsletter *HIV Treatment ALERTS!* debuts.





■ SMART study (Strategies for the Management of Anti-Retroviral Therapy) is launched on October 15, 2001. The study will follow 6,000 HIV-infected subjects for as long as 8 years and compares treatment strategies of continuous viral suppression versus intermittent therapy guided by CD4 counts.

■ With an intriguing twist on STIs, Tony Fauci and colleagues produce data on a potential “7 day on, 7 day off” STI regimen.

■ The 1st International AIDS Society Conference (“Conference on HIV Pathogenesis and Treatment”) is held in Buenos Aires, Argentina. The conference strategy is to alternate with the International AIDS Conference.

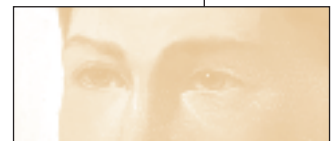
■ Ignoring recommendations from the Surgeon General, the Bush Administration mandates abstinence-only HIV prevention programs and targets programs that do otherwise for audits by the US Government.

■ Study team led by Steve Deeks publishes research in *The New England Journal of Medicine* showing that drug-resistant virus may not be as fit (able to reproduce itself, kill T cells, etc.) as wild-type virus. This is some good news for treatment-experienced patients, and consensus grows that staying on failing regimens (when no new treatment options are available) is better than stopping medications all together.



■ With the strength and durability of a Kaletra-based regimen now established, the idea of boosting other protease inhibitors with ritonavir (Norvir) gains popularity.

■ The 8th CROI, held in Chicago, is characterized by prolific studies on STIs. Disorders of bone metabolism are also discussed.



■ Pfizer division Agouron Pharmaceuticals swiftly ends its development collaboration on Immune Response Corporation’s Remune. The Immune Response Corporation eventually goes overseas to conduct further trials in larger populations.



2001

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2002

■ The FDA approves Zerit XR, a new once-daily version of Zerit (stavudine), which never comes to market.

■ UNAIDS reports that as of December 2002, women comprise about half of all people living with HIV/AIDS worldwide.

■ US National Intelligence Council releases report on the “Next Wave” of the epidemic, focused on India, China, Russia, Nigeria, and Ethiopia.

■ The FDA approves OraQuick Rapid HIV-1 Antibody Test, the first rapid test to use a finger prick.



■ The FDA approves a new 600-mg version of efavirenz (Sustiva) to reduce pill burden.

■ HIV is the leading cause of death worldwide, among those aged 15 to 59.



■ Bristol-Myers Squibb issues a warning regarding lactic acidosis in patients taking stavudine (Zerit, d4T).

■ On December 5, 2002, The CFA hosts the *2nd Basic Science Workshop on HIV*. The theme was novel therapeutic interventions.

■ May 27, 2002: Linda Grinberg, head of the Foundation for AIDS and Immune Research, dies.

■ Since December 2002, several reports have described kidney problems in patients taking tenofovir (Viread).

■ The AIDSinfo website (aidsinfo.nih.gov) is launched by the US DHHS for HIV/AIDS clinical trials and treatment information. The new site replaces the AIDS Clinical Trials Information Service (ACTIS, established in May 1989) and the HIV/AIDS Treatment Information Service (ATIS, established in October 1994).



2002

■ Research in the *Journal of Acquired Immune Deficiency Syndromes* documents the changing landscape of causes of HIV mortality. While decreases are observed in deaths from CMV, wasting, and HIV-associated dementia, increases are reported in deaths from sepsis, and diseases of the liver, kidney, and heart.

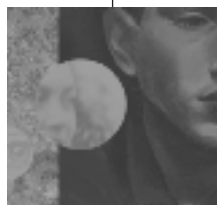
■ Pharmacogenomics, a new frontier in research, enters the HIV arena. Research begins to show that genetic differences influence such outcomes as efavirenz (Sustiva) effectiveness and abacavir (Ziagen) hypersensitivity.



■ Chiron Corporation announces it is terminating the SILCAAT trial because of business reasons. In the months following, the HIV research community and activists scramble to find a solution by sharing resources with ESPRIT and merging the two studies to ensure continuation of the IL-2 research.



■ June 2002: Save ADAP Committee is founded (part of ATAC).



■ Studies presented at the *14th International AIDS Conference* (“Knowledge and Commitment for Action”) in Barcelona, Spain continue to suggest that treatment during acute HIV infection (before testing positive for antibodies) may preserve the immune system.

■ ADAP under fire: 13 state AIDS Drug Assistance Programs (ADAPs) are forced to limit access to life-saving HIV medications for uninsured and underinsured Americans due to inadequate funding. An era of treatment “haves” and “have nots” in the US is ushered in.

- Some *9th CROI* (Seattle) highlights:
- Several adjunct therapies (including rosiglitazone) aimed at treating HIV lipodystrophy show little effect.
 - STIs may be dangerous in people with very low T cell counts (below 200 and especially below 50).
 - An estimated 850,000 to 950,000 people in the US are living with HIV, including 180,000 to 280,000 who do not know they are infected.

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2003



■ July 14: *The Guidelines for the Use of Antiretroviral Agents in HIV Infected Adults and Adolescents*, published by the US DHHS, is updated. The most striking change is the removal of a menu-style list of HIV medications from which a doctor could choose a main “anchor” drug (a PI or NNRTI) from one list and two “background” drugs (usually NRTIs) from another list for treating a patient. This is replaced with the actual recommendation of preferred regimens. The two preferred regimens are either:

1. Sustiva + Efavirenz + (Zerit or Viread or Retrovir), or
2. Kaletra + Efavirenz + (Zerit or Retrovir)

■ The FDA approves the first entry inhibitor enfuvirtide (Fuzeon, T20).

■ The FDA approves the PI atazanavir (Reyataz).



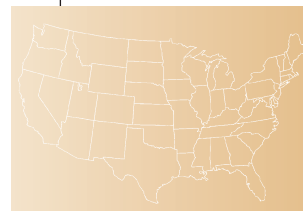
■ The FDA approves the PI fosamprenavir (Lexiva). Fosamprenavir is a pro-drug of amprenavir (Agenerase), and is converted into amprenavir in the body. The new formulation is easier to take because it requires much fewer pills.

■ The FDA approves the NRTI emtricitabine (Emtriva).



■ CDC statistics:

- The estimated number of AIDS cases diagnosed in 2003 in the US is 43,171.
- The cumulative number of AIDS diagnoses through 2003 is 929,985.
- The estimated number of people living with AIDS in the US is 405,926.
- The estimated annual number of deaths of persons with AIDS in the US is 18,017.
- The cumulative number of deaths of persons with AIDS through 2003 in the US is estimated at 524,060.



■ At the end of 2003, only 35 states are conducting state-wide HIV surveillance using the same confidential name-based methods as used for AIDS surveillance. Because national HIV surveillance does not yet exist, only estimated numbers of HIV cases are available. At the end of 2003, there are an estimated 761,790 people diagnosed and living with HIV or AIDS. There are an estimated 366,000 people diagnosed and living with HIV (not AIDS).

■ The William J. Clinton Presidential Foundation secures price reductions for HIV/AIDS drugs from generic manufacturers to benefit developing nations.



2003

■ UNAIDS Report:

- In 2003, almost 5 million people became newly infected with HIV, the greatest number in any one year since the beginning of the epidemic.
- At the global level, the number of people living with HIV continues to grow—from 35 million in 2001 to 38 million in 2003.
- In 2003, almost 3 million people died of AIDS. More than 20 million people have died since the first cases of AIDS were identified in 1981.

■ The South African Government announces a new antiretroviral treatment program.

■ L. Joel Martinez, a founder of The CFA, dies on November 12, 2003.



■ Interim analysis of study ACTG 5095 indicates that a triple-nuke regimen, in particular Trizivir, is not as effective as Sustiva-based regimens. Trizivir loses ground as a complete 3-in-1 regimen.

■ Community HIV/AIDS Mobilization Project (CHAMP) is founded (champnetwork.org).

■ “3 by 5” Initiative announced by WHO to bring HIV treatment to 3 million people by 2005.

■ Carlton H. Hogan dies on November 18, 2003.



■ The 10th CROI is held in Boston.

■ Bernard Hirschel declares the autovaccination hypothesis to be dead (*RITA!* Fall 2003).



■ President Bush announces PEPFAR, the President’s Emergency Plan for AIDS Relief, during the State of the Union Address. PEPFAR is a 5-year, \$15-billion initiative to address HIV/AIDS, tuberculosis, and malaria primarily in hard-hit countries.

■ The 2nd International AIDS Society Conference “Conference on HIV Pathogenesis and Treatment” is held in Paris, France.

■ December 2, 2003 (the day after World AIDS Day): Abbott Laboratories raises the price of Norvir by more than 400% and ensures that its own boosted product, Kaletra, becomes the cheapest boosted PI on the market.



■ Study CPCRA 064 confirms what many suspected—that STIs are dangerous in patients who have multi-drug resistant HIV. Although some smaller studies show more promising results, this is the beginning of work showing that STIs may not be beneficial, depending on the patient population.

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2004

■ Research presented by Steve Deeks (presented at *CROI*) and studies like PLATO (published in *The Lancet*) continue to show that patients with multi-drug-resistant (MDR) virus can achieve a survival benefit (for example, less CD4 decline and stable viral load) by staying on a failing drug regimen (for instance with NRTIs or PIs). The strategic use of drug resistance to minimize viral replication capacity/fitness and pathogenicity becomes a realistic approach to help patients with few treatment options stay alive longer.

■ The FDA approves Epzicom, a fixed-dose, once-daily, co-formulation of the NRTIs lamivudine (Epivir, 3TC) and abacavir (Ziagen).

■ The FDA approves Truvada, a fixed-dose, once-daily, co-formulation of the NRTIs emtricitabine (Emtriva, FTC) and tenofovir (Viread).

■ The FDA approves a generic version of didanosine (ddI) delayed release capsules (200 mg, 250 mg, and 400 mg). This is the first generic version of an HIV medication to be approved in the US.

■ US DHHS announces expedited review process by the FDA for fixed-dose combination and co-packaged products to be used by the US in purchasing medications under PEPFAR.

■ The FDA approves Sculptra to treat facial lipoatrophy.

■ Evidence suggests that the combination of didanosine (Videx) and tenofovir (Viread) is not optimal.

■ The 11th *CROI* is held in San Francisco.

■ The FDA approves the OraQuick Rapid HIV-1 Antibody Test for use with oral fluid.



■ The Global Fund to Fight AIDS, Tuberculosis, and Malaria holds first ever "Partnership Forum" in Bangkok, Thailand; 400 delegates participate.



■ The CFA, in collaboration with the Forum for Collaborative HIV Research, hosts the *Salvage Therapy II Think Tank* on April 16-17.

■ With several major phase II studies in progress or set to launch, hope for oral entry inhibitors is at an all-time high.

■ Group of 100 ADAP advocates from 30 different states travel to Washington, DC in February to ask lawmakers to consider a \$180 million emergency supplemental appropriation for ADAP.

■ Thousands of patients nationwide are on ADAP waiting lists as resources to cover medications no longer meet the need. Many states close enrollment, limit access to antiretrovirals, or anticipate program restrictions in the coming months. President Bush authorizes an emergency \$20 million for states with ADAP waiting lists—the equivalent of a band-aid for the problems being caused by severe shortfalls in ADAP funding.

■ UNAIDS launches The Global Coalition on Women and AIDS to raise the visibility of the epidemic's impact on women and girls around the world.

■ 2004 statistics from UNAIDS:

- The number of people estimated to be living with HIV/AIDS worldwide is 39.4 million.
- The number of people newly infected with HIV worldwide is an estimated 4.9 million.
- The annual number of deaths by AIDS worldwide is an estimated 3.1 million.

■ October 29, 2004: guidelines now recommend for HIV-positive patients who have never taken HIV medications before, have no symptoms, and whose T cell counts are over 350 should consider treatment when their HIV viral load reaches 100,000. The guidelines previously recommended considering treatment when viral load reached 55,000.

■ Charles Clifton, the Executive Director of Test Positive Aware Network (TPAN) in Chicago and Editor of *Positively Aware*, dies on August 15, 2004.

■ Keith Cylar, long time AIDS activist and co-founder and co-president of Housing Works, Inc., dies on April 5, 2004.

■ New website is launched for *AIDS Treatment News*, a respected HIV newsletter since 1986 (aidsnews.org).

■ 15th International AIDS Conference ("Access for All") is held in Bangkok, Thailand. This is the first International AIDS Conference to be held in Southeast Asia.

■ In December, Bristol-Myers Squibb and Gilead Sciences announce that they will work together to develop a fixed-dose combination of efavirenz (Sustiva, an NNRTI) and the NRTIs emtricitabine (Emtriva) and tenofovir (Viread)—all in one pill, once a day.



2004



■ An activist campaign is launched against Abbott in response to its 400% price increase for the PI ritonavir (Norvir), commonly used to boost levels of other PIs to improve potency and durability of PI-containing HAART. Notably, HIV-treating physicians join the campaign by barring Abbott representatives from their offices and refusing to consult with the company. A new group, Organized HIV Healthcare Providers (OHHP), is formed. For more information, visit atac.infovine.com/default/Abbottpricehike.asp or just Google "Abbott Norvir Price."



■ The controversial HIVNET 012 nevirapine (Viramune) study is endorsed by the WHO, UNAIDS, and other international organizations. NIH stands by the results, including the safety and effectiveness of the single-dose nevirapine regimen for preventing transmission to infants during birth.

■ New precautions are added to the labeling for the NNRTI nevirapine (Viramune). It should not be used in women with T cell counts greater than 250 or men with T cell counts greater than 400 because of the higher risk of developing liver damage.

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2005 (through June)

■ A new 500-mg tablet of the PI, Invirase, is now available to be used with ritonavir (Norvir) boosting.

■ In February 2005, the FDA approves the combination of Pegasys (peg-Interferon) and Copegus (ribavirin) for the treatment of HCV in HIV-positive patients. This treatment is the first one approved for patients co-infected with HIV and HCV.



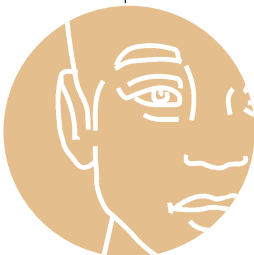
■ The FDA approves the PI tipranavir (Aptivus) to be taken in combination with ritonavir (Norvir) for patients who have virus that is resistant to other PIs.

■ On January 21, 2005, the CDC publishes new guidelines for the use of HIV medications to prevent HIV infection. Previously, post-exposure prophylaxis was only recommended for healthcare workers exposed to HIV. Now, HIV medications can be given to prevent infection after exposure to HIV through sexual intercourse, rape, injection drug use, or by accident.

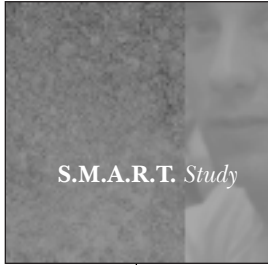
■ Warnings about using the PI Crixivan in HIV-positive pregnant women are published.

■ The CFA commemorates its 10th year and changes its name to “The Center for AIDS Information & Advocacy.”

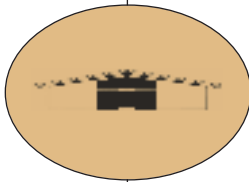
■ At a historic and unprecedented joint press conference, the WHO, UNAIDS, the US Government, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria announce results of joint efforts to increase the availability of antiretroviral drugs in developing countries. An estimated 700,000 people had been reached by the end of 2004.



2005 (through June)



■ March 2005: the SMART Study, continuing international expansion, reaches a halfway point and enrolls its 3000th patient. More than 200 US and international sites are enrolling patients.



■ The 12th CROI is held in Boston.



■ January 2005: Serono announces completion of patient enrollment in a phase III trial of its human growth hormone product Serostim for the treatment of HIV-associated lipohypertrophy. The primary goal of this trial is to assess whether Serostim induction therapy can reduce the abnormal accumulation of visceral adipose tissue and fat maldistribution seen in people with HIV/AIDS, and whether low-dose maintenance therapy prevents the abnormalities from returning during a continued course of therapy. More than 300 patients were enrolled in the study in 6 months.



■ The 3rd International AIDS Society Conference “Conference on HIV Pathogenesis and Treatment” is to be held in Rio de Janeiro, Brazil.

■ In May, more than 3,500 people living with HIV/AIDS and their loved ones from across the nation converge on Washington, marking the public step-off of the Campaign to End AIDS (C2EA). Protesters marched down Pennsylvania Avenue, then lined up 8,500 pairs of donated shoes in the street directly in front of the White House to symbolize the number of people worldwide who die of AIDS daily. The march was timed with the launch of a new website, endAIDSnow.org, which features a 21-point plan to halt the epidemic worldwide.

■ Study at 12th CROI by Walensky and colleagues reports 200 million years of life saved by HAART. Media quotes lead investigator as saying that HAART “can lengthen the life span of persons with AIDS by nearly 15 years.”



Ten years of HAART

By Mark Harrington

The year 1996 has brought a sea change in AIDS research and treatment. Three major factors have contributed to this sea change: a new understanding of viral pathogenesis, new and powerful antiretroviral treatment regimens, and new, more powerful tools for managing HIV levels in the blood and elsewhere in the body. Indeed, it was due to the sensitivity of these new viral load assays that researchers were able to determine the kinetics of HIV replication and immune system clearance within the infected human host, and devise new therapeutic approaches to reduce viral replication. The impact of viral load assays on HIV pathogenesis and treatment research can be compared to the impact of the Hubble Space Telescope on cosmology: both allowed researchers to see their subject with unprecedented resolution.

– Mark Harrington, *Viral Load in Vancouver*, 1996

Next year will mark a decade since the introduction of highly active antiretroviral therapy (HAART), which ushered in one of the most startling transformations in the history of medicine.

The Advent of HAART

By late 1995, the AIDS epidemic had been going on for 15 years. Despite years of activism and research, just 4 drugs—all of them nucleoside analogs (AZT, ddI, ddC, and d4T) had been approved to treat HIV. While AZT and its chemical cousins could delay HIV progression, none of them alone or in 2-drug combinations could durably control HIV, let alone reverse its associated immune suppression and threat of opportunistic diseases. The death toll from AIDS in the United States was approaching 50,000 per year and seemed to be rising.

HIV disease management appeared to be advancing at a snail's pace. Most people living with HIV would progress to AIDS and die, their progression only temporarily halted by 1- or 2-drug nucleoside analog therapy. At best, a cocktail of opportunistic infection (OI) prophylaxis drugs such as Bactrim, fluconazole, and azithromycin might be hoped to forestall the development of *Pneumocystis carinii* pneumonia (PCP), toxoplasmosis, cryptococcal

meningitis, and *Mycobacterium avium* intracellulare (MAC), while a number of other OIs remained horribly undertreated or untreatable.

The first reports suggesting that protease inhibitors (PIs) might be different were thought to be drug-company hype. TAG's coverage of the 1995 *Interscience Conference on Antimicrobial Agents and Chemotherapy* (ICAAC) conference described a small Abbott study:

Participants were given AZT/ddC/ritonavir. Their CD4s went up by 100 and their plasma RNA went down by 2.5 logs at 20 weeks. Over the subsequent weeks, he claimed, an increasing proportion of participants became viral culture negative—which is to say, they could not culture infected cells from the blood. “Some became PCR and culture negative, which suggests that the viral reservoir was empty.”

At the time, we described this as an “irresponsible, unsubstantiated claim” (*TAG Does ICAAC*, 1995).

The 8 months after November 1995, however, witnessed approval by the US Food & Drug Administration (FDA) of 5 new anti-HIV drugs—the nucleoside analog 3TC, 3 new PIs—saquinavir (Invirase), zidovudine (ZDV), and zalcitabine (Zalcitabine).

(Crixivan)—and the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (Viramune). Moreover, that year saw the introduction of new, quantitative viral load assays—such as Roche’s RNA PCR and Chiron’s branched-chain DNA (bDNA) test—which could reliably measure the amount of HIV in the bloodstream.

Many forces contributed to the HAART revolution. AIDS activism certainly played a part in multiple ways—by demanding faster AIDS research, mobilizing national awareness, and pressuring Congress to increase funds for clinical trials. Basic science on the biology of HIV infection clarified the key role of HIV in depleting CD4 cells. Studies funded by the National Institutes of Health (NIH) demonstrated both the uses and the limitations of available nucleoside analog reverse transcriptase inhibitors (NRTIs). Drug companies invested in a variety of new treatments for both HIV and its associated infections and cancers. Among the most crucial factors was the role of the FDA in permitting expanded access to experimental AIDS therapies beginning with AZT in 1986, which perhaps most critically provided a framework for accelerated approval of AIDS drugs, beginning with ddI in 1991 and codified in federal regulations in 1992. Accelerated approval allowed drugs to be approved based on favorable changes in surrogate markers such as measurements of CD4 cells and later, viral load. Indeed, ddI was approved in 1991 based on a very small rise in CD4 cells (11 cells over baseline in the ddI group versus a continued decline in those on AZT) in an AIDS Clinical Trials Group (ACTG) study, 116B/117, which compared ddI to AZT among AZT-experienced individuals. The clinical benefits of ddI were confirmed in the same study by early 1992. Soon after, ddC was approved in mid-1992 based on similar changes, which did not however confer clinical benefit.

The problem with CD4 cell changes as a surrogate marker was that CD4 cell count was a direct marker of a person’s immune status, but only an indirect marker of anti-HIV drug activity (it rose when HIV levels fell). The CD4 cell changes associated with

NRTIs were modest and often transient. And the available blood tests for HIV levels in the early 1990s were primitive.

By 1995, however, pivotal papers by groups from the University of Alabama and the Aaron Diamond AIDS Research Center (ADARC) showed that ritonavir—a member of a new class of drugs, the PIs, which interfered with a different stage of HIV’s life cycle than the NRTIs—could reduce HIV levels in the blood by 2 logs (99%)—as measured by new quantitative HIV RNA tests such as the polymerase chain reaction (PCR).

While the longer-term benefit of triple-combination antiretroviral therapy (ART) was not yet clear, in the short-term, falling HIV RNA was associated with rising CD4 cells and reductions in incidence of AIDS and death. In Abbott’s pivotal ritonavir study, which randomized 1,090 HIV-infected persons with CD4 counts below 100 cells/mm³ to ritonavir or placebo over a background of NRTIs, 119 ritonavir recipients developed AIDS or died versus 205 (37.5%) placebo recipients during a median follow-up of just 29 weeks (Cameron 1998). In March 1996, ritonavir became the first AIDS drug since AZT in 1987 to win full approval based on a reduction in mortality. The problem with the approach used in the Abbott study became clear within a few months, however—simply adding a PI into a background of what later would be considered a failing NRTI background. Despite the potency of the PI, the emergence of resistance to ritonavir became widespread. Even worse was the fact that HIV resistant to ritonavir was often resistant to indinavir—Merck’s equally potent PI—as well.

Nonetheless, the short-term clinical benefit and longer-term promise of the PIs appeared clear. The FDA approved Roche’s saquinavir in December 1995. It was weak and had low bioavailability (4%), yet when combined with two NRTIs (AZT and ddC, again) was clearly superior to AZT+ddC on their own. Perhaps more important for AIDS treatment in the long run was FDA’s approval of lamivudine (Epivir, 3TC) in November 1995. Because of its low

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toxicity, good pharmacokinetics (eventually being approved for once-daily use) and the fact that 3TC-resistant HIV was less fit and mutated more slowly than wild-type HIV, 3TC eventually became the most commonly used drug in HIV combination therapy.

When FDA Commissioner David Kessler—an appointee of the first President Bush who stayed in office until the mid-Clinton years—heard about the favorable results of the Abbott study (due to Abbott's FDA filing for full approval), he asked Merck to submit its PI, indinavir, to the FDA for accelerated approval at the same time. Both drugs were approved in March 1996. Each was a very potent drug with significant drawbacks. Ritonavir, taken at the full dose of 600 mg twice daily, had high gastrointestinal (GI) toxicity, while indinavir had to be taken thrice daily on an empty stomach, requiring people to undergo 3-hour, food-free windows each day, while downing liters of water to prevent the development of kidney stones (nephrolithiasis).

By the time of the *11th International Conference on AIDS*, held July 8–11, 1996 in Vancouver, British Columbia, researchers from a variety of groups—the ADARC, Boehringer Ingelheim, Merck, and Abbott—showed that various 3-drug antiretroviral combinations—AZT and 3TC plus ritonavir or nelfinavir (Viracept), AZT and ddI plus nevirapine, or even ritonavir plus saquinavir without any reverse transcriptase inhibitors—could reduce HIV levels in the bloodstream by over 99% to below limits of detection (ranging from less than 500 to less than 25 HIV copies per milliliter of blood)—in a substantial majority (70% to 100%) of those treated. The studies, while small and short-term, demonstrated that dramatic reductions in viral load could be seen among individuals with either acute or chronic HIV infection, among antiretroviral-naïve people, and even among those who had been exposed to prior therapy. In Vancouver, John

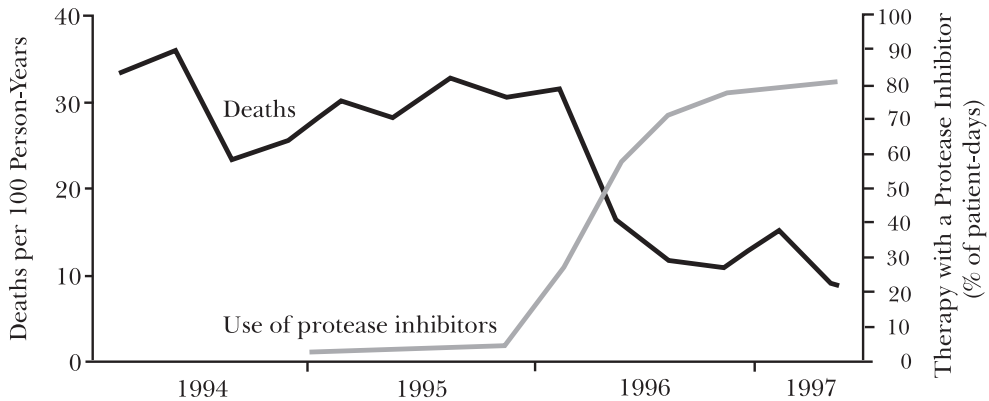
Mellors from the Multicenter AIDS Cohort Study (MACS) presented the famous study demonstrating that viral load in chronic infection predicts rate of progression to AIDS (Mellors 1996), and David Ho and Marty Markowitz presented their famous eradication hypothesis, suggesting that if HIV levels in the peripheral blood could be suppressed by combination antiretroviral therapy (ART) for several years, residual amounts of integrated HIV provirus in human cells might eventually be eliminated from the body (Ho 1996, 1998).

At the time, TAG pointed out the unanswered questions:

*The duration of long-term viral suppression remains to be determined. . . . The most potent, tolerable regimen(s) for long-term suppression need to be determined, and rational sequences. . . need to be defined. Studies in patients with higher CD4 levels and relatively low viral load need to compare partial versus apparently complete plasma RNA suppression as an initial strategy, or immediate versus deferred suppression. Simpler, more convenient regimens need to be developed to enhance compliance, eg with the use of time-release drugs which can be taken once daily or less often. Studies to optimize long-term compliance with complicated, inconvenient regimens need to be conducted, covering a range of strategies in a diverse set of populations. Interventions which may contribute to replenishment of holes in the immunologic repertoire. . . need to be designed and implemented. When and whether people experiencing a significant CD4+ T cell rise after combination therapy can be removed from opportunistic infection (OI) prophylaxis and maintenance needs to be addressed. Finally, research needs to be conducted to determine the feasibility of treating or eradicating HIV disease among infected persons in developing nations (TAG, **Viral Load in Vancouver**, 1996).*

What is remarkable is that even in the first months of 1996, before anyone really knew how to best use PIs in combination therapy, AIDS deaths began to drop dramatically in the US, as shown in these data from the HIV Outpatient Study:

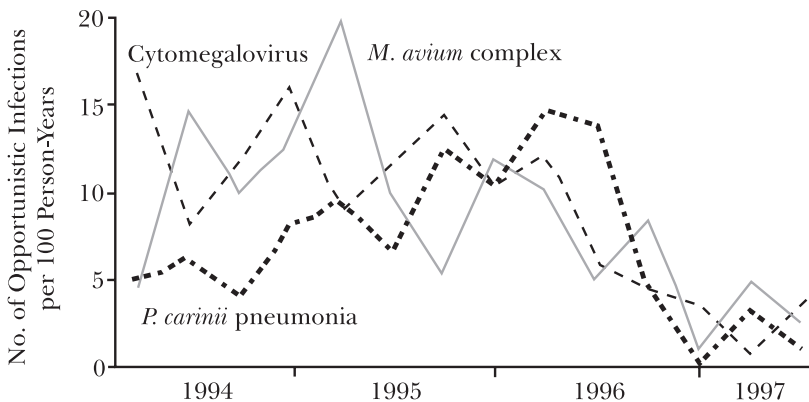
AIDS mortality and PI use, 1994 – 1997 (HIV Outpatient Study)



Mortality and frequency of use of combination antiretroviral therapy including a protease inhibitor among HIV-infected patients with fewer than 100 CD4+ cells per cubic millimeter, Jan. 1994–June 1997 (Palella 1998).

Common AIDS-related OIs dropped dramatically as well:

Declining CMV, PCP, & MAC, 1994 – 1997

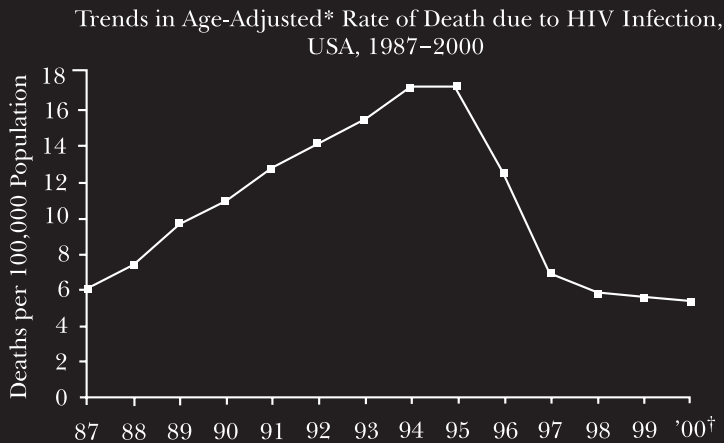


Rates of cytomegalovirus infection, *Pneumocystis carinii* pneumonia, and *Mycobacterium avium* complex disease among HIV-infected patients with fewer than 100 CD4+ cells per cubic millimeter, January 1994–June 1997 (Palella 1998).

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As the following data show, the decline in AIDS deaths in the US was dramatic, falling almost 3 fold between 1995 and 1998, and stabilizing thereafter.

AIDS deaths in US, 1987 – 2000



* Using the year 2000 US standard population.

† Preliminary mortality data for 2000

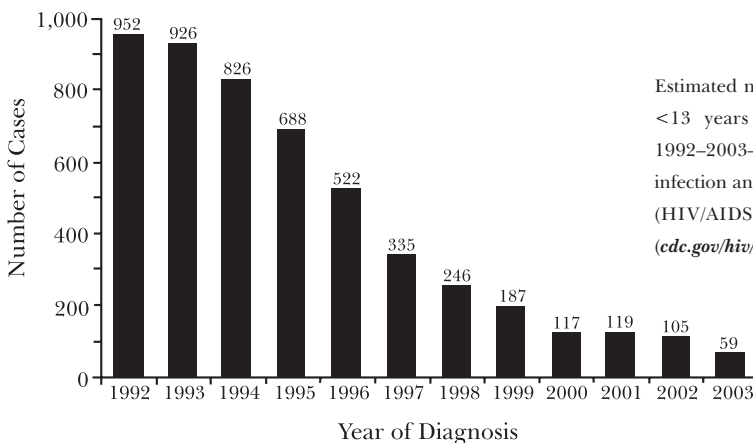
Year

Note: For comparison with data for 1999–2000, data for 1987–1998 were modified to account for *ICD-10* rules instead of *ICD-9* rules.

Data from CDC.

Spurred in part by HAART and perhaps even more by the introduction of AZT to prevent mother-to-child transmission (MTCT), perinatal HIV infection rates declined by over 90% and pediatric AIDS diagnoses went from 952 in 1992 to just 59 in 2003.

Decline in Pediatric AIDS Diagnoses, US, 1992 – 2003



Estimated numbers of AIDS cases in children <13 years of age, by year of diagnosis, 1992–2003—United States—Cases of HIV infection and AIDS in the United States, 2003 (HIV/AIDS Surveillance Report, Vol. 15) (cdc.gov/hiv/stats/2003SurveillanceReport.htm)

Consolidation of the HAART approach

Following the euphoria of Vancouver, with a regrettable but predictable media over-emphasis on the possibility of eradication of HIV with HAART, came the much harder work of developing and disseminating solid, evidence-based guidance for physicians, care providers, people living with HIV, and insurers. This work began in late 1996 when the Department of Health and Human Services (DHHS) set up not one but 2 panels to develop “Principles of HIV Therapy” and “Guidelines for Antiretroviral Therapy.” The first panel was set up by NIH’s Office of AIDS Research, the second by the Office of HIV/AIDS Programs (OHAP) in the Department. Their work was published in the *Morbidity and Mortality Weekly Report (MMWR)* in 1998. The DHHS Guidelines Panel became an ongoing body, meeting by conference call monthly and in person annually at the Retrovirus Conference. The Guidelines were updated frequently and sometimes significantly.

When to start ART – 1998

Reflecting the exuberance of Vancouver, the initial recommendations for when to start ART were:

- Any symptomatic HIV infection (AIDS, thrush, unexplained fever), regardless of CD4 count and viral load
- Asymptomatic with CD4 count < 500 cells/mm³ or HIV RNA $> 10,000$ (bDNA) or $> 20,000$ (RT-PCR) copies/mL – “Treatment should be offered. Strength of recommendation is based on prognosis for disease-free survival.”
- Asymptomatic with CD4 count > 500 cells/mm³ and HIV $< 10,000$ (bDNA) or $< 20,000$ (RT-PCR) copies/mL

– *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults & Adolescents, MMWR 47/RR-5, 24 April 1998*

At the time, no one knew the duration of ART-induced viral suppression, how complete immune reconstitution might be, or whether there would be long-term side effects, and if so, what they would be.

By the late 1990s, however, reports began emerging, first in a trickle, then in a flood, of new and apparently horrible side effects associated with antiretroviral therapy. These ranged from so-called “Crix-belly” to “buffalo hump” to facial lipoatrophy/visceral fat accumulation/peripheral fat wasting (“lipodystrophy”), to a complex of possibly mitochondrial-DNA-dysfunction-associated effects such as lactic acidosis and hepatosplenomegaly to—also seen before HAART—peripheral neuropathy and myopathy. It was initially unclear and, in some cases still, is less than completely understood to what extent these side effects were related to individual drugs versus drug classes. Certainly, however, in combination with the increasing evidence that HAART could sometimes reverse (and not just delay) the progression of HIV-related immune suppression, the pendulum began to swing from “hit early, hit hard” to “hit HIV-1 hard, but only when necessary” (Harrington & Carpenter 2000).

Many clinicians were still taken with the “hit early” approach, but in the absence of controlled clinical trials defining the optimal point at which to start therapy, and the emergence of data from several large cohort

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studies including the British Columbia cohort, the EuroSIDA cohort, and the CASCADE collaboration, it appeared that the benefits of HAART were clearest when started before CD4 counts dropped below 200 cells/mm³. However, the benefits of beginning at various CD4 strata above that level were less clear. Greater knowledge about toxicity and the importance of life-long adherence also promoted a change in the starting strategy. The DHHS Guidelines Panel changed its recommendations on “When to start” in 2002, and by 2005 they were rather more conservative:

When to start? – 2005

AIDS-defining illness	Any CD4	Any viral load	Treat
Asymptomatic	CD4<200	Any viral load	Treat
Asymptomatic	CD4>200<350	Any viral load	Treatment should be offered following full discussion of pros and cons with each patient
Asymptomatic	CD4>350	>100,000	Deferring treatment is recommended
Asymptomatic	CD4>350	<100,000	Defer therapy

– aidsinfo.nih.gov/guidelines/adult/AA_040705.pdf, Table 4

The debate about whether to continue recommending use of 2 NRTIs without a potent PI backbone was more or less ended when the results of ACTG 320 were announced in early 1997. The study showed that among 1,156 HIV-infected persons with fewer than 200 CD4 cells, the combination of AZT with 3TC and indinavir reduced the incidence of AIDS and death by 50% compared with those taking AZT with 3TC alone. The study provided clear evidence that the HAART approach prolonged health and life in this population, and that its benefits were associated with sustained viral suppression and increases in CD4 counts, often to above 200.

Later evidence came from multiple studies showing that among persons whose CD4 counts rose above 200 cells/mm³, it was safe to stop taking prophylaxis and even maintenance therapy for *Pneumocystis carinii* (now *Pneumocystis jirovecii*) pneumonia (PCP), toxoplasmosis, cytomegalovirus (CMV) retinitis, fungal infections, and MAC. Thus, there was clinical evidence that HAART could in fact restore holes in the immune repertoire, even if not always completely.

Major additions to the drug armamentarium came in 1998 with efavirenz (Sustiva), in 2000 with lopinavir/ritonavir (Kaletra), in 2001 with tenofovir DF (Viread), and—arguably—in 2003 with enfuvirtide (Fuzeon, T-20), the first fusion inhibitor, and with atazanavir (Reyataz). Efavirenz catapulted the NNRTI class to first-line therapy along with the PIs; its sponsor, Dupont, boldly compared efavirenz to the gold-standard PI, indinavir, in its pivotal study Dupont 006, which demonstrated that efavirenz was as potent as indinavir while being less toxic and, at once rather than 3 times daily, easier to take as well. Lopinavir/ritonavir also emerged as a new first-line drug after proving to have greater potency, better pharmacokinetics,

FDA antiretroviral approval dates

Drug	Brand name	Sponsor	Approval date	Class
AZT (zidovudine)	Retrovir	Burroughs-Wellcome (now GlaxoSmithKline)	19 Mar 1987	NRTI
ddI (didanosine)	Videx	Bristol-Myers (now Bristol-Myers Squibb)	9 Oct 1991	NRTI
ddC (zalcitabine)	Hivid	Hoffmann-LaRoche	19 Jun 1992	NRTI
d4T (stavudine)	Zerit	Bristol-Myers Squibb (BMS)	24 Jun 1994	NRTI
3TC (lamivudine)	Epivir	GlaxoSmithKline (GSK)	17 Nov 1995	NRTI
saquinavir (SQV)	Invirase	Hoffmann-LaRoche	6 Dec 1995	PI
ritonavir (RTV)	Norvir	Abbott	1 Mar 1996	PI
indinavir (IDV)	Crixivan	Merck	13 Mar 1996	PI
nevirapine (NVP)	Viramune	Boehringer Ingelheim	21 Jun 1996	NNRTI
nelfinavir (NFV)	Viracept	Agouron (now Pfizer)	14 Mar 1997	PI
delavirdine (DLV)	Rescriptor	Pharmacia & Upjohn (now Pfizer)	4 Apr 1997	NNRTI
AZT/3TC	Combivir	GSK	27 Sep 1997	NRTI
saquinavir sgc*	Fortovase*	Hoffmann-LaRoche	7 Nov 1997	PI
efavirenz (EFV)	Sustiva	DuPont (now BMS)	17 Sep 1998	NNRTI
abacavir (ABC)	Ziagen	GSK	17 Dec 1998	NRTI
amprenavir (APV)	Agenerase	GSK	15 Apr 1999	PI
lopinavir (LPV)/ ritonavir	Kaletra	Abbott	15 Sep 2000	PI
ddI enteric coated	Videx EC	BMS	31 Oct 2000	NRTI
AZT/3TC/ABC	Trizivir	GSK	14 Nov 2000	NRTI
tenofovir DF (TDF)	Viread	Gilead	26 Oct 2001	NRTI
enfuvirtide (T-20)	Fuzeon	Hoffmann-LaRoche / Trimeris	13 Mar 2003	EI
atazanavir (ATV)	Reyataz	BMS	20 Jun 2003	PI
FTC (emtricitabine)	Emtriva	Gilead	2 Jul 2003	NRTI
ABC/3TC	Epzicom	GSK	2 Aug 2003	NRTI
FTC/TDF	Truvada	Gilead	2 Aug 2003	NRTI
fosamprenavir	Lexiva	GSK	20 Oct 2003	PI
ddI delayed release (generic)	-	Barr Laboratories	3 Dec 2004	NRTI
tipranavir (TPV)	Aptivus	Boehringer Ingelheim	22 Jun 2005	PI

* soft gel capsule saquinavir (Fortovase) will be discontinued by Roche by February 15, 2006.

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and a higher barrier to resistance than other PIs. Tenofovir had the benefits of a long half-life and apparently reduced toxicity compared with other NRTIs. T-20 was a breakthrough drug from a scientific perspective, but its clinical use was limited by being a twice-daily injectable, with painful injection site reactions. And although BMS's atazanavir reduced cholesterol levels compared with other PIs, and could be taken once daily, its potency was inferior unless combined with ritonavir, which mitigated its cholesterol benefits for some, while increasing its potency overall.

Regimen simplification came with the introduction of fixed-dose combinations including Com-bivir (AZT+3TC, 1997), Trizivir (AZT+3TC+ ABC, 2000), Epzicom (ABC+3TC, 2003), and Truvada (FTC+TDF, 2003); however, these advances were blunted to some extent by their being—in Joep Lange's words—"incestuous combinations" developed because they had the same manufacturer, rather than because they made intrinsic therapeutic sense.

By 2005, results from several long-term studies indicated clear favorites among the NNRTI and PI classes for initial therapy, along with better NRTI backbone regimens. With this amount of choice in first-line regimens, it is perhaps not a surprise that there is less clarity with respect to second-line and salvage therapy regimens. Most treatment switching currently occurs because of side effects and involves changing one drug within a regimen or simplifying regimens. For instance, changing to a once-daily regimen to simplify the regimen, rather than for virologic failure or the emergence of drug resistance.

The use of resistance testing is another novelty which interceded over the past 5 years; however its benefits in clinical practice as compared with the intelligent use of treatment history guided by expert opinion have yet to be clearly demonstrated in clinical trials.

Feasibility of HIV eradication

Starting in 1997, a number of research teams from Baltimore, San Diego, and elsewhere demonstrated that despite HAART's potent effects in limiting HIV replication, slowing the emergence of drug resistance and supporting immune reconstitution, the impact on integrated proviral DNA that existed in more than 100,000 resting but infected CD4 cells was negligible, and would not lead to viral eradication within a normal human lifespan. Drastic therapeutic techniques such as whole body T cell ablation "therapy" followed by immune cell transplants (carried out in an understandably small number of patients) failed to yield anything to justify their toxicity. The possibility of HIV eradication awaits a breakthrough in our understanding of HIV pathogenesis and immune therapy.

Future therapy for HIV

The best new drugs to emerge since 1996 are all members of the first 3 established drug classes, the NRTIs, NNRTIs, and PIs. However the best new drugs to emerge in the coming decade are likely to be members of new drug classes such as the several entry inhibitors (EIs)—CCR5 (R5), CXCR4 (X4), gp120, and fusion inhibitors—and possibly even newer approaches such as integrase, budding, and maturation inhibitors. The coreceptor blockers—R5 and X4 antagonists—must surmount fears of their effects on HIV tropism and demonstrate lack of significant toxicity. In addition, the introduction of either an R5 or an X4 antagonist might require the addition of an expensive new diagnostic test—the viral tropism assay that currently costs over \$1,000—to the standard of care. As the experience of the past decade shows, adding a new test—such as viral load, resistance, or even therapeutic drug monitoring (TDM)—is expensive, time-consuming, and beset by difficulty, particularly if the additional clinical benefit attributable to the test is difficult to demonstrate as in the case of resistance testing or controversial as with TDM, widely used in Europe but not in the United States.

What to start? – 1998

Recommended ARV agents for treatment of established HIV infection

Preferred: Strong evidence of clinical benefit and/or sustained suppression of plasma viral load:

One choice from column A and column B. Drugs listed in random, not priority, order:

<i>Column A</i>	<i>Column B</i>
Indinavir	AZT + ddI
Nelfinavir	d4T + ddI
Ritonavir	AZT + ddC
Saquinavir SGC*	AZT + 3TC
Ritonavir + Saquinavir SGC* or HGC*	d4T + 3TC

Alternative: Less likely to provide sustained virus suppression

1 NNRTI (Nevirapine) and 2 NRTIs (column B, above)
Saquinavir HGC* + 2 NRTIs

Not generally recommended: 2 NRTIs

Not recommended: All monotherapies
d4T + ddI
ddC + ddI
ddC + d4T
ddC + 3TC

* SGC denotes soft-gel capsule (Fortovase) and HGC denotes hard-gel capsule (Invirase).

What to start? – 2005

Preferred regimens

NNRTI-based Efavirenz + (3TC or FTC) + (AZT or TDF)
PI-based Lopinavir/ritonavir + (3TC or FTC) + AZT

Alternative Regimens

NNRTI-based Efavirenz + (3TC or FTC) + (ABC or ddI or d4T)
Nevirapine + (3TC or FTC) + (AZT or d4T or ddI or ABC or TDF)*

* but NVP not recommended in women with CD4 > 250 or men > 400

PI-based Atazanavir + (3TC or FTC) + (AZT or d4T or ABC or TDF or ddI)
Fosamprenavir + “ + “
Indinavir/ritonavir + “ + “
Lopinavir/ritonavir + “ + “
Nelfinavir + “ + “
Saquinavir/ritonavir + “ + “

3 NRTI based ABC + AZT + 3TC only when a preferred or an alternative NNRTI-based or a PI-based regimen cannot or should not be used

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Ultimately, lifelong combination chemotherapy for HIV is far from ideal. As yet unproved are approaches to strengthen the immune system by using cytokines such as interleukin-2 (IL-2) or interleukin-7, therapeutic vaccines (which are beset by the same problems afflicting preventive HIV vaccine research), or other therapeutic strategies such as intermittent therapy (which might reduce total drug exposure while preserving drug benefit).

HIV research is well funded and the new anti-retroviral pipeline is fairly robust—TAG's anti-retroviral drug pipeline chart, available online at aidsinfonyc.org/tag/tx/pipeline2005.html, shows up to 20 drugs currently in clinical trials that may make it to FDA review within the next few years, with many more in pre-clinical stages of development. However, as the long saga of AIDS research to this date indicates, the most promising

approaches will come from new insights derived from basic science. Unfortunately, the next few years do not look as promising as the last decade for AIDS research. Funding at the NIH, the engine of global funding for HIV research, will be climbing by just 2% next year, compared with the more than 100% increases registered since 1992. More AIDS funds will go to vaccine research, which is an urgent priority, but less likely to result in immediate breakthroughs. Industry investment, while still healthy, depends on a robust basic science base whose future is no longer guaranteed. Finally, the US and global healthcare systems are in a state of flux, far from ideal, and deeply unjust for many here and most internationally. And the task of providing treatment to those who need it worldwide, and keeping them on therapy for decades to come, has only just begun.



Mark Harrington is a founder and Executive Director of Treatment Action Group (TAG) in New York (aidsinfonyc.org/tag). He was awarded a MacArthur Fellowship in 1997.

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HIV/AIDS research after HAART

By Robert C. Gallo, MD

The success in therapy against HIV with HAART has been more than most of us could have hoped for, even allowing for the fact that one group claimed the possibility of eradication of the virus in 1995. However, most scientists knew such therapy would be needed for life, and that some toxicity and drug resistance were predictable. Nonetheless, the overall success of HAART has made HIV/AIDS the “flagship” among viruses and viral disease for antiviral therapy, proving for the first time that if we know sufficient detail of the molecular mechanism of viral replication, then effective antiviral therapy is achievable. I make this point because pharmaceutical companies (and academic scientists) in the mainstream had abandoned antiviral research in the 1970s, because of the prior lack of success and the knowledge that unlike bacteria and other unicellular microbial parasites, viruses have no metabolism of their own and are highly dependent upon the cell’s machinery for their replication. In short, therapy had to be more specific and in general more sophisticated.

HAART therapy was born from a sophisticated understanding of HIV replication. It had its origins in the 1970s with elucidation of the replication cycle of animal retroviruses, especially the discovery of reverse transcriptase (RT), and by the findings that drugs that inhibit replication of animal retroviruses even prevented disease in animals (mice) by blocking transmission of a mouse retrovirus from a pregnant mouse to its offspring. But going from mouse to man was far from simple or obvious because of the thinking that drug toxicity and drug resistance would be too problematic. Indeed, no one had ever shown efficacy of antiretrovirals in animals infected

with retroviruses over a protracted period. Thus, the historic contribution of the development of AZT in the mid-1980s by Burroughs-Wellcome and The National Cancer Institute cannot be overstated. This set the stage for many groups, especially many pharmaceutical companies, to develop other RT inhibitors.

RT, of course, is an enzyme necessary for HIV replication and carried by the virus. Consequently, it was natural also to try to find inhibitors of other enzymes—more or less specific to HIV and essential to its replication. The protease of HIV was an obvious target. Proteases of animal retroviruses and their biological function had been characterized years earlier in animal retroviruses and in the first human retrovirus to be discovered, the leukemia-causing retrovirus called HTLV-1. This was subsequently done with the HIV protease. Its structure was elucidated by scientists, and they began to test inhibitors of this enzyme. This led to the introduction of protease inhibitors in the clinic. Combination with RT inhibitors was a “no brainer” and was instituted rapidly by many clinicians in the US and Europe, collaborating with drug companies in what would soon emerge as the major advance we call HAART. This is the origin of HAART, although only in the broadest conceptual context.

What has occurred over the past 10 years since the development of HAART has been less exciting but more fundamental in our understanding of HIV. Because of drug resistance and toxicity, we knew we would need to continue basic research on HIV and attempt to develop additional approaches to therapy. In this regard, substantial advances, with practi-

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cal implications in my view, have emerged from 3 general areas: 1) more details of HIV replication and of cellular factors that work against HIV, 2) greater understanding of HIV pathogenesis, including people who resist HIV infection, and 3) a realization that we can target not only viral but also cellular factors needed by the virus.

As to the future, basic studies of HIV replication will continue to be needed because we will continue to need new therapies, but I believe we should not and will not be limited to approaches that target steps in HIV replication. New therapies will also come from studies of pathogenesis and of the immune response to infection. Some therapies will target cellular factors (required by HIV, but to some extent dispensable by our cells, or at least factors which the cell is less dependent upon than the virus). The advantage of targeting cellular factors is that they are far less mutable than HIV proteins and therefore less likely to have escape mutations. Though it is still possible that HIV “strains” could emerge that avoid utilization of the particular cellular factor, this should present more of a challenge for the virus.

The details of HIV replication that now have the most pregnant implications are related to early steps of HIV infection. With a far greater understanding of the HIV cell entry process, we can now envisage HIV entry inhibitors as whole new classes of drugs for the future. Each of the now-known several steps in the entry process can be targeted, but I am most excited by the possibility of antagonists of the key portal of entry of most HIV infections, CCR5. This cellular protein is present on the surface of some cells. It is particularly abundant on activated T cells, and its normal function is to receive signals from some of the human molecules called chemokines. It so happens that the HIV envelope protein uses this molecule to initiate most HIV infections. It is important to recall that some people are born without CCR5 and are healthy, ie,

CCR5 does not seem to be needed by modern humans. It may be dispensable for us, but usually not for HIV. This presents a new and exciting target for HIV therapy, and we should see this emerge in the near future. However, as stated above, CCR5 antagonists are not the limit. There are several steps to HIV entry into the cell, and several of these can, have been, and will continue to be targeted.

Newly discovered cellular factors that counter HIV infection have also been identified, and these too offer new approaches for future therapy. One of these is called APOBEC-3G, a cumbersome term, but an important cellular protein that helps disable HIV under some circumstances. It is predictable that some scientists will seek to enhance or mimic its activity in the future. And there are others. In other words, I foresee the future as including many new approaches to treat HIV infection, and these new approaches will increasingly include cellular factors that we may either enhance or inhibit to control HIV.

Over the past 10 years, studies of HIV pathogenesis (other than viral entry into cells) that have both impressed me the most and seem to offer therapeutic possibilities include the observations that 1) abnormal activation of the immune system is a central feature of HIV disease, 2) lasting damage is produced very early in infection, 3) “knock out” of T cells in the gut during acute infection is an early and pathogenetically important aspect of HIV infection, and 4) uninfected T cells are also substantially impaired and may die prematurely, apparently more so in the chronic phase of infection. This leads us to consider 1) the therapeutic use of drugs that diminish lymphocyte activation (cyclosporine being the prototype), 2) treating HIV as early as possible, and 3) finding the mechanisms involved in impairing uninfected T cells and attempting to do something about it. For example, working with Daniel Zagury in Paris, we have come to the conclusion that the HIV Tat protein is impor-

tantly involved in the impairment of uninfected T-cells. Therapeutic vaccines targeting the Tat protein are underway with promising preliminary results. I think this and some other rationally designed therapeutic vaccine trials will offer alternative or additional therapeutic approaches. The upside of such an approach (compared to HAART) is a lack of toxicity and probably less resistance by HIV. The downside is less power in reducing HIV replication and viral load as compared to HAART.

So, can we eradicate HIV? It is conceptually possible, but may not be doable in the next decade. Even if so, it would likely be limited to very few. Eradication can be approached by 2 paths: the first (and the one now pursued in some clinics) is to vigorously treat active infection with HIV drugs, the second is to target the remaining latently infected T cells (“the reservoir”). These cells harbor silent HIV genomes, which can later be activated and give rise to new viruses as these cells enter loci that have the capacity to induce T cell activation because of their cytokine milieu. Some clinical scientists seek to use chemicals to activate latently infected cells in advance. In so doing, these cells expose themselves to the therapists’ arsenal that “destroys” HIV-producing cells. They will do this while using drugs that prevent new HIV infections, eg, entry inhibitors and RT inhibitors. The alternate, more sophisticated, and more “down the road” approach is to use molecular probes that seek, find, and destroy cells harboring HIV genomes—even those hidden in the cell as silent DNA proviruses. I do not envisage the latter such approach becoming a reality for at least another decade, and I do not believe

the former approach will succeed; though it is worth the major effort being invested. Consequently, I am not an optimist about near-term eradication.

As for an HIV preventative vaccine, I believe it is achievable, but in my view it will take another 7 to 15 years. The current and soon to be tried candidates will likely not be effective. Most, if not all, are vaccines that induce cell-mediated immunity (CMI), but for more than 20 years, I have argued that a vaccine candidate must approach or realize complete blockade of HIV infection at the site of cell entry. CMI-based vaccines do not achieve this. Rather, they allow infection to occur with the hope that the CMI response will keep HIV levels low enough that disease will not occur. I think such viruses will eventually escape. That is why I think we need to completely prevent infection right at the level of HIV entry. This means obtaining neutralizing antibodies, which in turn means an envelope-based vaccine. These antibodies must be broad enough to inhibit various strains of HIV. This was impossible with the kind of envelope vaccine developed by VaxGen, and therefore, it predictably failed. The antibodies also must be sustained, because HIV, as a retrovirus, integrates its genes into human DNA shortly after infecting a cell. This provides little or really no time for an immune response to be recalled. These are truly unprecedented, high hurdles for us to overcome. However, because of the great increase in our understanding of HIV entry, I think we now have insights as to what approaches may bring success.

Robert C. Gallo, MD, *co-discovered HIV as the infectious agent that causes AIDS. He is Director of the Institute of Human Virology at the University of Maryland Biotechnology Institute, as well as a Professor in the Department of Microbiology Immunology and a Professor in the School of Medicine at the University of Maryland, Baltimore.*



Therapeutic and diagnostic advances in the HAART era

By Ben Cheng

It has been almost 10 years since the approval of the first protease inhibitor, saquinavir (Invirase) in December 1995. Since that time, there have been great advances in treatment monitoring, treatment strategies, and overall knowledge about the pathogenesis of the disease, but we are still far from a cure and the virus continues to outsmart all the advances that have been made.

Results from the first-generation protease inhibitor—saquinavir, zidovudine (AZT), and zalcitabine (ddC)—combination studies were greeted with much excitement as they showed a profound effect on survival and ability to control virus replication. Starting in 1996, several studies and cohorts demonstrated dramatic decreases in mortality and opportunistic infections with the widespread availability of the protease inhibitors. The term “HAART” (highly active antiretroviral therapy) was first used around this time.

The use of viral load testing in studies investigating the protease inhibitors was another cause for excitement. These tests, using polymerase chain reaction (PCR) or branched DNA (bDNA) technology, offered a more direct method of measuring the treatment effect on the virus in blood, as well as other tissue compartments, compared to measuring p24 antigen or CD4 cells. For the first time, it was possible to measure how quickly viral load (HIV levels) dropped with the initiation or switch of therapy and to determine when a treatment regimen was starting to lose effectiveness as indicated by a rebound in viral load. The availability of the protease inhibitors and viral load testing resulted in a paradigm shift in how people with HIV were treated.

The initial protease inhibitor studies clearly showed that people had to be very adherent when taking these medications. There was a massive effort by community-based organizations, as well as the research establishment and the pharmaceutical companies, to promote adherence.

The results from studies with protease inhibitors were met with so much enthusiasm that many researchers were discussing the possibility of eradicating the virus from a person’s body. Different strategies were explored from using 4 or more drugs for people who recently became infected to using drugs to “flush out” the reservoirs and then using HAART. However, none of these strategies were successful and the work by Bob Siliciano examining the half-life of the virus in latently infected cells further demonstrated how difficult it would be to eradicate the virus.

With the introduction of 3 protease inhibitors within a few months of each other, there was tremendous marketing pressure from the 3 companies that manufactured these products, leading to intense debates among the companies involved. One area of concern dealt with the potential resistance and cross-resistance to these drugs. It was not until the results from ACTG 333 were announced, showing that there was indeed cross-resistance between these drugs, that the issue was resolved. This experience taught the community to be very skeptical about how data were presented. Another lesson learned was that the less drug resistance is studied and the earlier the drug is put into clinical development, the better the drug looks. It has become an unfortunate reality for most of the drugs that many “problems” are discovered only after it has been

more extensively studied or been on the market for a few years.

The early excitement generated with the protease inhibitors soon turned to more guarded optimism. Many people did not achieve durable virologic benefits from these drugs, mainly because they had previously taken and developed resistance to the nucleoside analog reverse transcriptase inhibitors (NRTIs). As a result, they were virtually being treated with protease-inhibitor monotherapy. It also became evident that these drugs came with their own set of side effects. Ritonavir caused nausea and diarrhea, and indinavir caused kidney stones. Saquinavir did not cause many side effects, mainly because the drug was poorly absorbed and in comparison to the other 2 protease inhibitors, did not produce as large a viral load reduction. It soon became clear that to get maximal virologic benefit from the protease inhibitors, they had to be combined with 2 drugs, or at a minimum one new drug that the individual had not previously taken, and that these new drugs could not be cross-resistant with any of the drugs that were previously used.

Several strategies were explored for people who had few or no treatment options. Many groups reported some virologic success with a megaHAART or multidrug rescue therapy (combining 4 or more drugs). However, these regimens were generally not well tolerated and drug interactions made these regimens difficult to manage. Another strategy with reported early success was Structured Treatment Interruptions (STIs). The goal was for individuals to stop their antiretroviral therapies to allow drug-resistant HIV to revert back to wild-type virus and then start a megaHAART regimen. Small short-term studies showed a good virologic response. However, larger studies indicated that this strategy was actually potentially harmful, as people taking an STI were more likely to experience an opportunistic infection and disease

progression compared to those continuing on a HAART regimen.

Another problem with many of the early protease inhibitors was the complicated dosing schedule. Many of these drugs had to be taken 3 times a day, making adherence especially challenging for many people. The middle dose was particularly difficult for people who had jobs and especially since many of these drugs also had food requirements. One strategy to achieve twice-daily dosing with the protease inhibitors was to exploit the inhibitory effects of ritonavir on the cytochrome p450 3A4 enzymes. Ritonavir has a potent effect on the cytochrome p450 3A4 enzymes in the liver such that when it is combined with another protease inhibitor (or any drug that is metabolized or affected by this enzyme), drug levels of the other drug are dramatically increased and the resultant lowered metabolism causes the other drug to stay in the body for a longer period. The use of lower doses of ritonavir significantly increased the levels of saquinavir and indinavir while allowing for twice-daily dosing.

Several companies also developed new formulations of existing drugs in an attempt to overcome some of the problems encountered with the original formulations. Hoffman-LaRoche developed an “improved” version of saquinavir (Fortovase) and GlaxoSmithKline developed fosamprenavir (Lexiva) to replace amprenavir (Agenerase). Interestingly, Hoffman-LaRoche is now moving back to the original Invirase formulation of saquinavir (with a new 500-mg tablet) because it is better tolerated than the Fortovase version when the drug is combined with ritonavir. Other companies have also developed new dosage forms, such as Agouron (Pfizer) with a 625-mg nelfinavir (Viracept) formulation.

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Another strategy to simplify dosing regimens was to combine different drugs into a single pill. The first was Combivir, which is a combination of zidovudine (Retrovir, AZT) and lamivudine (Epivir, 3TC). In developed countries this is usually only possible when one company makes all of the drugs. Although even this is changing with the recent announcement by Bristol-Myers Squibb and Gilead Sciences that they will combine tenofovir (Viread), emtricitabine (Emtriva), and efavirenz (Sustiva) into a single, once-daily pill. In the developing world market, where much of the drug supply is produced by Indian generic manufacturers, fixed dosed combinations are much more common.

Yet another strategy that was explored, because of the complexities of taking protease inhibitors, was to start people naive to antiretroviral therapy on an induction phase, which consisted of at least 3 drugs. After their viral loads were undetectable for a number of months, patients switched to a maintenance phase of 2 drugs. But a French study and a US study both showed that participants who tried this approach had viral load rebounds more rapidly than participants who started and continued on a 3-drug regimen.

The commercial availability of genotypic and phenotypic resistance testing provided another advance as a way to understand which drug(s) in a treatment regimen was no longer active. However, interpretation of the resistance tests as a means of selecting a new regimen remains problematic even today. These interpretation algorithms are usually put together by a group of experts based on the most recently available data; however, since new data is released constantly, these algorithms are always slightly behind the most current knowledge.

In the early years of HAART, the appearance of body shape changes such as buffalo humps,

enlarged bellies, sunken cheeks, and loss of fat in the arms and legs among people with HIV were attributed to the protease inhibitors. Additionally, many people on the protease inhibitors had elevated cholesterol and triglyceride levels, as well as elevated liver enzymes. These factors and the results from the Dupont DMP 006 study showing that efavirenz (Sustiva) was superior to indinavir, resulted in a very rapid shift in how the protease inhibitors were used. Instead of being used as part of a first-line regimen, they were now considered as second- or even third-line regimens. Even though other studies showed that elevations in triglyceride and cholesterol and body shape changes were also seen with the other classes of drugs and not just the protease inhibitors, the field had moved to using a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen as part of first-line therapy.

More recently, a new assay to determine the replication capacity of HIV is being studied. While it remains to be seen how to best use the results from this assay in everyday practice, some of the preliminary results have been intriguing. Results suggest that HIV that is resistant to some drugs, especially 3TC and the protease inhibitors, does not replicate as well as wild-type virus. The implications of these findings are that people who have failed their treatment regimen might consider remaining on their failed regimen as the virus is replicating poorly. However, the flip side of such a strategy is that the virus will continue to mutate and eventually may replicate as well as wild-type virus. Furthermore, the additional mutations may confer cross-resistance with other drugs from the same class.

Another area that is being actively being researched is therapeutic drug monitoring. The goal of this approach is to ensure that specific drug levels are within the target concentration—high enough to

achieve maximal viral suppression and avoid drug resistance but not too high (so as to minimize side effects). Similarly, pharmacogenomics is being actively researched. It has been widely known that people of different ethnicity and gender metabolize drugs differently. Pharmacogenomics might, in the future, help predict who might be at risk for developing side effects or who might require a higher or lower dose of a particular drug.

The recent intriguing results from a couple of small studies using lopinavir and low-dose ritonavir (Kaletra) monotherapy may result in a new paradigm shift. Since the introduction of the protease inhibitors and HAART, the recommendation has always been to start therapy with 3 drugs. If the larger studies confirm the results from the smaller studies, it may be possible to take Kaletra as monotherapy when starting antiretroviral therapy for the first time.

New drugs and especially new classes of drugs are needed to help those with limited treatment options. The approval of the fusion inhibitor T-20 (enfuvirtide, Fuzeon) now means that there are 4

classes of drugs available. Several other new classes of drugs are currently being investigated in clinical studies including the CCR5 antagonists, CXCR4 antagonists, and integrase inhibitors. Furthermore, there are several immune-based therapies and therapeutic vaccines in the clinical trial phase. These therapies, while not acting directly against HIV, may boost the immune system to control HIV and may allow people to stop their antiretroviral therapy for a period of time.

While there have been great advances made in the treatment of HIV in the developed world, not everyone in the US is able to access the new medications and diagnostic tests. Budget cuts and the increasing costs of new therapies and diagnostics now means that many people in the US have no or limited access to these advances. Moreover, the availability of these new medications and diagnostic tests has not transferred to the developing world, where the vast majority of people with HIV live. It is important to continue the advances with new diagnostics and new therapies, but it is vital that people have access to the new technologies or therapies as soon as they are commercially available.

Ben Cheng is the Deputy Director of the
Forum for Collaborative HIV Research in Washington, DC (hivforum.org).



HAART at 10: An interview with Joseph Gathe

Joseph Gathe, Jr, MD, is an HIV-treating physician and clinical researcher. He is the Medical Director of the Donald R. Watkins Memorial Foundation in Houston.

RITA: Highly active antiretroviral therapy (HAART) is almost 10 years old. What do you think has been the greatest lesson we've learned about HIV treatment in the last 10 years?

JG: We've learned several lessons. First, we've learned that an orchestrated, scientific response can lead to control of a critical disease when great minds come together. But this is a two-edged sword. We cannot rest on any laurels, and this is a learning process that cannot end. The great boon for HAART has been the ability to keep people alive, but there have been evolving side effects and other aspects of therapy that we could not foresee. We must be circumspect and cautious in the future for the sake of patients. Smart people can make a difference, but we could never have anticipated the ramifications of the drugs once they were being used in the real world.

RITA: Do you think HAART has taken the spotlight from, or possibly even derailed, other promising research or treatment advances?

JG: Not really, but there has been some complacency among scientists and activists alike resulting in a reduced urgency for finding other ways to approach the treatment paradigm. HAART has bought us time; we are

sitting in the oasis and can take a drink for a moment. But we need vaccines (both preventive and therapeutic). We need better ways to achieve immune reconstitution in the setting on HIV infection. It's disheartening that there is not more dialogue between virologists and immunologists. This may or may not be on account of the success of HAART. What we have achieved with HAART is reaching its maximum efficiency. Our approach to really improve patient outcomes has to be different (immune approaches, vaccines, etc.) People are dying in different ways, not from the typical opportunistic infections seen more frequently in the earlier days of AIDS. I see cancers, heart attacks, organ failure and other manifestations—even in younger patients—that I attribute to a “premature aging” of patients and incomplete immune restoration.

RITA: What has HAART not delivered?

JG: HAART has delivered time, but it has not delivered a cure. Also, it has not delivered the ability to effect long-term management of HIV-positive patients with the current treatment paradigm. In diabetes, insulin can be given over a long period of time without adverse side effects or toxicities. HAART over a long time can be toxic, not to

mention expensive. If we do not achieve a cure, then we need long-term and affordable solutions to HIV disease.

RITA: Many people characterize HIV (at least where HAART is available) as a “chronic, manageable” condition—what’s your take on this?

JG: I think it is chronic and manageable. When a new patient comes in, that’s what I say—mainly because the patients I see think this is a death sentence. They need to understand that if they take care of themselves and play this correctly, then an extended life expectancy is possible. HIV today is more like diabetes than, say, cancer, but it must be closely monitored. Most of all, we need to instill hope in patients.

RITA: What about the less pretty side of HAART (side effects, toxicities, drug interactions, lipodystrophy, etc.)? How does this affect your ability as a clinician to treat this disease?

JG: This impacts my practice greatly. A patient’s T cells and viral load may be fine, but mentally, this person can be in bad shape. With something like lipodystrophy, patients may avoid being out in public, for example. This is something that must be overcome in a physician-patient relationship. One thing that can be done is working to prevent this from happening in the first place by carefully selecting antiretroviral agents. But some big questions still exist. Is this caused by the treatments, or the disease, or both? The pendulum of thought for early versus later treatment is still moving. You can’t wait too long before treatment, otherwise damage from HIV could predispose patients to a variety of risks even in the setting of HAART. We need more studies looking at the “new endpoints” of HIV: liver dis-

ease, kidney failure, lipodystrophy/metabolic effects. This is not about opportunistic infections or AIDS anymore. And, these are the issues that patients care about.

RITA: Where do you think HIV treatment will be in another 10 years?

JG: I *hope* we will be able to use treatment for short periods of time, and then use immune-based therapy such as a therapeutic vaccine to control the virus over longer periods of time. But here’s my greatest fear. In my practice, I see 3 or 4 newly diagnosed patients each week. This is during a time when healthcare resources in general are being cut, and HIV care is not being supported in the same ways as in the past. Not only will quality of care decline, but I feel that there are no new generations of researchers, and especially clinicians, coming forward in this field. People are moving to industry and other more profitable areas. When the group that’s in their mid- to late 40s moves on, there may not be people to replace them. This could further relegate the disease to the backburner. We need more manpower. I’m very disturbed by this trend.

RITA: Some people view the entry inhibitors in development as the next great hope in HIV treatments, possibly replacing some classes of antiretroviral agents as first-line treatments: a second-generation HAART, if you will. How do you view the possibility of “HAART II”?

JG: I view it as a mixed bag. I have great hope because we need new classes of drugs, and these entry inhibitors *may* have fewer toxicities overall. However, my greatest concern is that these agents may not be able to stand

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alone and may have to be combined with agents that act within the cell anyway. I have concerns about patients whose virus is not purely CCR5-tropic, even though agents like TNX355, enfuvirtide (Fuzeon), and CCR5 antagonists may all be combinable. Also, there are concerns about pre-existing resistance to various agents when trying to construct viable regimens.

RITA: Speaking of drug resistance, it's a problem. But indications of drug-resistant HIV with decreased viral "fitness" and "replicative capacity" are showing a different side of drug resistance. Do you think we can reach a time when achieving certain HIV mutations would actually be a therapeutic strategy?

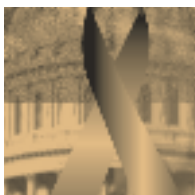
JG: No question about it. With new patients, I have 5 goals:

1. To control viral load
2. To improve CD4 T cell count
3. To try to prevent the development of resistance if possible
4. To direct any resistance that does develop down the "path" that I prefer
5. To pick the most logical partner medications (those with proven efficacy and durability) and not just combine any drugs. HIV resistance can be a friend or a foe. I believe in making it a friend, for example trying to induce hypersensitivity to non-nucleoside

reverse transcriptase inhibitors (NNRTIs) by capitalizing on the maintenance of resistance to nucleoside agents. This can result in improved virologic responses to an NNRTI-based regimen. We have enough evidence to start using such approaches in the clinic.

RITA: Finally, do you ever think there will ever be a cure for HIV?

JG: No. (But I still hope there will be!) First of all, viral illnesses do not typically get "cured." We may develop vaccines to prevent them, they may run their course and be cleared by the immune system, or they may establish a chronic latency that persists through the host's lifetime. What I hope can one day happen (as was demonstrated in work presented at the *Conference on Retroviruses and Opportunistic Infections* a few years ago, where monkeys with SIV remained healthy despite having high viral loads) is that we can exploit how to down-regulate the ability of the immune system to react to HIV. If we could somehow turn off immune hyperstimulation that results in chronic cytokine dysfunction, tissue damage, etc., then perhaps the virus would be more latent, such as in cytomegalovirus or Epstein-Barr virus infections. If we do not find a cure, then establishing a long-term, "symbiotic" relationship that minimizes immune damage would be desirable.



HAART at 10: An interview with Cal Cohen

Cal Cohen, MD, is an HIV-treating physician and clinical researcher. He is Research Director of the Community Research Initiative of New England and the HIV Clinical Management Consultant at Harvard Vanguard Medical Associates in Boston.

RITA: Highly active antiretroviral therapy (HAART) is almost 10 years old. What do you think has been the greatest lesson we've learned about HIV treatment in the last 10 years?

CC: Probably the realization that HIV can (but not always will) be controlled potentially for a normal lifespan—at least much closer than what we had imagined before HAART.

RITA: Do you think HAART has taken the spotlight from, or possibly even derailed, other promising research or treatment advances?

CC: No, actually I do not. It's fair to say that the work that went into antiretrovirals made HAART successful—it *earned* the spotlight. We went from having dramatic success with HAART in the 1990s, to dealing with the challenges of HAART, to developing more safe and durable success in HIV-positive patients today. Sure, other potential therapeutic approaches have not gone ahead as fast, but this is not because of HAART being in the spotlight.

RITA: What has HAART not delivered?

CC: HAART is lacking in that we need more confidence in its safety. There are cosmetic issues, organ toxicities, etc. and these vary

between individuals. We certainly don't want people looking sicker than they are because of issues like fat wasting; that is a tough price to pay. The promise of newer medications—if they are less toxic—is that people will look as good as their numbers.

RITA: Many people characterize HIV (at least where HAART is available) as a “chronic, manageable” condition—what's your take on this?

CC: It's basically true, but, of course, not for everyone. At this point, we know what it takes to control virus (plus, whatever immune-based therapies may eventually be able to offer). Even though some research is showing, for example, a 17% increase in the relative risk of a heart attack in patients taking HAART, this is not as bad as the days when much higher percentages of patients suffered from other issues, like peripheral neuropathy. Clearly, progress is being made, but HAART is still not as good as it needs to be.

RITA: What about the less pretty side of HAART (side effects, toxicities, drug interactions, lipodystrophy, etc.)? How does this affect your ability as a clinician to treat this disease?

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CC: What do you mean?

RITA: In other words, compared to other diseases, how does the HAART paradigm measure up?

CC: The field of HIV has had tremendous advancement on a continuous basis (at least, when compared with other fields). But we are still learning the rules of the game. Other diseases have had decades of work behind them and are therefore more “mature.” In the field of HIV, we are less confident of our decisions at this point. In cancer, we know to treat periodically. In diabetes, we know to treat every day. But in HIV, there is an uncertainty that simply won’t be answered for years to come. In the meantime, we need drugs that stay up to date with the challenges of this epidemic, whether that is adherence difficulties or toxicity. Studies like the CPCRA’s SMART Trial (Strategies for the Management of Anti-Retroviral Therapy) may eventually provide us with more answers. In HIV, there is still room for creativity at this point.

RITA: Where do you think HIV treatment will be in another 10 years?

CC: There are a number of things happening right now to help answer that question.

1. Continued development of medications that are simpler, safer, and more effective. In several cases, we are down to regimens comprising 2 pills once a day, and we are looking to do even better. What about not taking medications every day? Maybe 5 out of 7 days is good

enough. Smaller or longer “breaks” may be possible. Research will bear this out. In the area of initial therapy, we can continue to be proud of our progress, in light of what starting therapy was like even just 5 years ago. However, there are still ambiguities as to when treatment should be started.

2. Continued interest in other ways to simplify therapy. An example of this would be the induction/maintenance scenario. Perhaps with newer, more potent drugs, we can start with 3 medications to achieve viral control and then maintain control with fewer drugs.
3. Ongoing lessons of how *not* to create resistant virus. Resistant virus is being spread, and there will still be patients dealing with the damaging effects of resistant virus because of limited treatment options. I hope that immune-based therapies will one day be able to compensate for the limitations of antiretroviral medications when it comes to viral resistance—not to replace HAART, but to be used together in combination to achieve better and more balanced control of infection.
4. Efforts to treat the world, rather than the rich of the world. AIDS is an international issue, and the US is not exempt. If we are not capable of treating our own citizens, then how can we contribute to the global crisis? HIV must be a priority. Tax cuts must be balanced with public health; initiatives for smaller government

involvement must be balanced with the collective good.

RITA: Some people view the entry inhibitors in development as the next great hope in HIV treatments, possibly replacing some classes of antiretroviral agents as first-line treatments: a second-generation HAART, if you will. How do you view the possibility of “HAART II”?

CC: HAART is a goal and cannot be defined in terms of classes of medications or specific agents. As we have seen over the past 10 years, HAART evolves. Newer agents tend to be better than earlier ones. The same things may happen with newer classes. What we want is a safe, durable way to curb the damage caused by uncontrolled HIV infection. While the actual principle of HAART may not change, how it’s accomplished will change. Certainly for the next 5 years, we will be expanding the repertoire and therefore expanding ways to accomplish the goals of therapy in terms of what combinations to use, when to use them, how we might rotate drugs, etc.

RITA: Drug resistance is a problem. But indications of drug-resistant HIV with decreased viral “fitness” and “replicative capacity” are showing a different side to drug resistance. Do you think we can reach a time when achieving certain HIV mutations would actually be a therapeutic strategy?

CC: In some ways, this already is a therapeutic strategy, but it’s not completely reliable. HIV often pays a price to mutate. Resistance sometimes weakens the virus, but sometimes the virus can compensate

and overcome this effect. Capitalizing on viral resistance is not always a reliable strategy. If there was a reliable way to control the virus this way, then we’d have a much easier time with treatment. However, while we know resistance can slow this virus down—we all know resistant virus can win; look at what happened in the era of treating with just nucleoside reverse transcriptase inhibitors (NRTIs) and the ongoing deaths from uncontrolled HIV. We are getting smarter about resistance, though. We know that resistant virus with reduced replication capacity is better than stopping medications entirely. We can preserve CD4 T cells to some degree using resistance as a tool—until better options come along. To me, this is a second-best strategy, but I am certainly not trying to minimize its importance when it is the best we can do.

RITA: Finally, do you ever think there will ever be a cure for HIV?

CC: Sure. I’m willing to think so. I don’t know who will develop it, how it will come to be, or what it will involve. But it is important for everyone involved in this field to *imagine* that a cure is possible. I am not even convinced it will happen in my lifetime, but I can maintain that it’s at least plausible. If not, then we just close the door on this epidemic. Two years ago, Bill Clinton spoke at the annual *Conference on Retroviruses and Opportunistic Infections* and said that if researchers do their job in terms of science, and politicians do their job in terms of access, then perhaps HIV will one day flow from our blood into the history books where it belongs.



Domestic treatment access in 2005

Warning: Do not read this without the aid of a good antidepressant!

By Lei Chou

Ten years of HAART have taught us some painful lessons. As the community adjusted its hopes down from early predictions of viral eradication to a reality of life-long maintenance therapy, we have had to absorb the impact of long-term drug toxicities and face the demands of medication adherence. We are reminded that available drugs don't work for everyone as we have watched the clocks run out on our loved ones, and we have waited as scientific conferences come and go with no major breakthroughs. While we've become numbed to the deadly consequences of willful inaction on the part of industry and government globally, we are exhausted by the constant struggle for publicly funded treatment access here at home. The failure of our government to address the public health disasters created by the lack of universal healthcare continues to be amply illustrated by this epidemic.

Since the approval of the first protease inhibitors, there has been an uphill battle for adequate funding for the AIDS Drug Assistance Program (ADAP). Appropriated annually under the Ryan White CARE Act, ADAP funding levels are set at the discretion of the Administration and Congress. The waning commitment to domestic HIV care has led to inadequate funding for the past 5 years, with program waiting lists and access restrictions spreading across the country. As the payer of last resort, ADAP was designed to help those without other means to access lifesaving treatment. The lack of funding has placed thousands of patients at the mercy of drug company charity programs, if they have the support system to help navigate the various and varying requirements.

The Bush Administration has conducted an assault on Medicaid since the President came into office. This federal entitlement healthcare program for

the very poor and disabled is relied upon by more than half of the people living with HIV/AIDS (PWAs) in the country. Led by the Administration and under the guise of "cost containment," the latest salvo this summer involves the Congress and state Governors in re-writing the entitlement by imposing mandatory co-pays and premiums for prescriptions and services. These proposed policies would disproportionately impact long-time survivors the most, those who are likely to be living on limited disability checks and need multiple prescriptions and frequent doctor visits.

While the new Medicare Prescription coverage taking effect in 2006 may help some higher income elderly Americans, the effect on those living with HIV will be very different. Sixty thousand PWAs on Medicare who have been getting their drugs through Medicaid will lose this comprehensive coverage on January 1, 2006, and be moved to limited private drug plans. Another 20,000 PWAs who do not qualify for Medicaid may lose their ADAP coverage depending on the state in which they live, and they will likely face higher co-pays, premiums, and thousands of dollars of out-of-pocket costs before qualifying for "catastrophic" coverage. The complicated transition between programs coupled with flat Ryan White funding for case management will likely be chaotic and could potentially lead to treatment disruptions for those least able to afford it.

Behind this dire landscape are drug companies that continue to raise drug prices at twice the rate of inflation, on top of pricing every new drug 20% to 50% higher than existing drugs in the same class. Those lucky enough to have private insurance are also no stranger to the effect of high prices, as co-pays and premiums reach outrageous highs as

insurance companies attempt to pass the increases on to individual policyholders. While any reasonable price control legislation looks unlikely to materialize as long as our politicians remain in the deep pockets of the drug industry and its powerful lobby, we taxpayers are the ones paying for it. Access to treatment based on the ability to pay cannot be accepted as another ugly reality of HAART. As we mark the passing of HAART's tenth year, don't forget about the people we are leaving behind. The "new face" of AIDS in the US is that of the patient who, regardless of race, gender, or social standing, cannot access lifesaving care in the wealthiest country on Earth.

Help fight for domestic treatment access by joining the following national grassroots working groups:

To help fight for ADAP funding, join the Save ADAP Committee of the AIDS Treatment Activists Coalition (atac-usa.org), contact Ryan Clary at rclary@projectinform.org.

To help fight federal Medicaid cuts and to improve Medicare, join the HIV Medicaid & Medicare Workgroup by contacting Lei Chou at leichou@champnetwork.org.



Lei Chou is the Director of Mobilization at the Community HIV/AIDS Mobilization Project (CHAMP): champnetwork.org.

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- HIV Treatment Alerts!
- Houston-area HIV/AIDS Clinical Trials Directory
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