

Medications for HIV disease have become increasingly advanced, affording many patients to live well into middle- and- old age.



Issues

Treatment Advances

The Ryan White HIV/AIDS Program ensures people living with HIV/AIDS have access to the latest treatments, including life-saving AIDS medications. Advances in vaccine and pharmaceutical research promise new ways to treat, and perhaps halt, HIV infection in the future.

HRSA's Response to HIV Treatment Advances*

For more than two decades, Ryan White HIV/AIDS Program grantees have rapidly implemented life-saving advances in HIV care and treatment in their clinics, under the guidance of the U.S. Department of Health and Human Services (HHS), Health Resources and Services Administration (HRSA), HIV/AIDS Bureau (HAB). The Ryan White HIV/AIDS Program is the payor of last resort for poor, uninsured, or underinsured HIV-positive people in the United States. But grantees are far more than gap-fillers: They are extraordinary for both the range and quality of services they offer. Years of dedication and hard work have built a medical home for people living with HIV/AIDS (PLWHA) who have nowhere else to turn.

PLWHA often face multiple hardships, such as poverty, unstable housing, incarceration, and stigma as well as addiction and other medical and psychiatric comorbidities. From the beginning, HRSA recognized and developed the capacity to address the medical and psychosocial needs of PLWHA. Ryan White-funded programs provide patient-centered HIV primary care, medications, mental health care, addiction treatment, case management, transportation, and other ancillary services proven to be essential for keeping people in care.^{4,5} As Brian Feit, public health analyst in HAB's Technical Assistance Branch, notes, "We built a system that would hold people as they got sicker. Lo and behold, it was the system we needed to keep people alive."

Although the program itself is administered by HAB, the Federal Government has always made community involvement a cornerstone of its implementation at the State and local levels. Planning Councils and Consortia, for example, are comprised in part by consumers who reflect the demographics of the local epidemic. Participation of PLWHA is essential for identifying and prioritizing community needs; making decisions to allocate funds; and creating short- and long-term plans for service coordination, delivery, and oversight.

* This essay is not meant to be an exhaustive summary of all HIV medications but rather a discussion about the Health Resources and Services Administration's HIV/AIDS Bureau in the context of major HIV/AIDS treatment advances.

Snapshot: Demographics of the HIV Epidemic in the United States

According to the U.S. Centers for Disease Control and Prevention, there are more than 1 million HIV-positive people in the United States. People of color and the poor are hardest hit: HIV is 7.6 times more prevalent among Blacks, and 2.6 times more prevalent among Hispanics than Whites. It is twice as common among people living below the poverty line than among those above it.^{1,2}

HIV Treatment Timeline

“At the beginning of the epidemic, there was no treatment. We didn’t talk much about the future,” recalls Linda Frank, a public health professor and HRSA AIDS Education and Training Center (AETC) faculty member. “We were just watching people die.” Both the prognosis and the standard of care for HIV infection have changed since those early years. Antiretroviral therapy (ART) has dramatically lowered HIV-related morbidity and mortality in the United States.^{6,7,8}

By 2006, highly active ART (HAART) had increased life expectancy among PLWHA in the United States by so much that the combined total is equivalent to 3 million years of life.⁹ But when the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act (also called the Ryan White HIV/AIDS Program) was enacted in 1990, the only approved treatment for HIV/AIDS infection was a single antiretroviral drug, AZT (zidovudine). Clinicians fought to stave off opportunistic infections and administered palliative care. “When I started working as a nurse in 1984, all you could do for people with AIDS was to help them die as comfortably as possible,” says Diana Travieso Palow, chief of HAB’s HIV Education Branch in the Division of Training and Technical Assistance. “People have forgotten,” she says.

Research efforts had yet to lead to better treatments or a cure for HIV/AIDS, but basic science began to bear fruit. Researchers were learning more about HIV and AIDS. They discovered that instead of remaining dormant for approximately a decade, HIV was actively replicating in infected lymph nodes and gradually depleting the immune system through several different mechanisms.¹⁰

1994: Preventing a Killer

Countless lives were saved by the January 7, 1994, approval of bactrim as prophylaxis against *pneumocystis pneumonia* (PCP), a serious opportunistic infection occurring in 70 to 80 percent of AIDS patients. PCP was a leading cause of death in the pre-HAART era; the fatality rate ranged from 20 percent to 40 percent.¹¹ Since then, the incidence of PCP has plummeted in the United States as a result of earlier initiation of HIV treatment and use of prophylaxis in people with severe immunosuppression.¹² Now, the bulk of PCP cases occur in people who are unaware of their HIV status, who are out of care, or who have a CD4 cell count of <100 cells /uL.¹³

1994: Preventing Mother-to-Child Transmission

On February 21, 1994, a breakthrough was announced: Interim results from the Pediatric AIDS Clinical Trials Group (ACTG) study 076 found mother-to-child transmission (MTCT) of HIV could be prevented. When AZT was given to HIV-positive pregnant women and their infants, transmission dropped from 25.5 percent to 8.3 percent (a 67.5 percent reduction).¹⁴ Previously, the rate of MTCT ranged from 15 to 40 percent.^{15,16} “The beautiful thing about ACTG-076 was that it was the first evidence-based, scientific study with good news,” says Travieso Palow.

From the beginning, Ryan White HIV/AIDS Program staff and grantees worked to quickly disseminate research findings and translate them into clinical practice. Program staff participated in the development of U.S. Public Health Service (PHS) recommendations, released in August of 1994, for AZT use to prevent MTCT and of the subsequent recommendation for voluntary HIV counseling and testing for pregnant women, released in 1995.^{17,18} At the same time, HRSA issued guidance on reducing MTCT, thereby providing grantees with strategies to implement the PHS recommendations. To further extend their reach, HRSA also began to support onsite and online technical assistance for clinic staff through the National HIV Pediatric Resource Center. Continuing those efforts, Ryan White funding supports the national, 24-hour perinatal HIV hotline, where clinicians can get advice and referrals to local specialists.

“HIV/AIDS is the best example of translational research,” says Barbara Aranda-Naranjo, director of HAB’s Division of Service Systems. “Results from ACTG-076 were brought



to the most affected communities almost instantly because we had immediate access to the patients.” The Ryan White HIV/AIDS Program staff made huge efforts to ensure that HIV-positive pregnant women could understand and benefit from the ACTG-076 study. They did more than deliver care—they built a community.

“After ACTG-076, we were pushing for pregnant women to know their HIV status and begin AZT to prevent babies from getting HIV,” explains Travieso Palow. “It was difficult because AZT made many pregnant women feel sick and gave some of them anemia. In South Florida’s Haitian community, this fueled rumors that AZT was poison,” she adds. To counter misinformation, “Our Haitian staff members went on the radio to get the message out that AZT was not poison and that it could prevent babies from contracting HIV,” says Travieso Palow. This kind of community based, culturally appropriate outreach and education has been a hallmark of the Ryan White HIV/AIDS Program. Travieso Palow recalls,

We became the family of choice for many HIV-positive Haitian, Latina, and African-American pregnant women who were rejected when they disclosed their HIV status to family, friends, or partners. They had no support system. They knew we would maintain their [confidentiality](#) and that our nurses, social workers, and case managers were there to provide support. I can’t tell you how many times we stayed very late and made follow-up calls. We watched these women become empowered through talking with each other at our support groups. Some became advocates.

By 1996, the number of perinatally infected children dropped to 480 from a peak of 1,650 in 1991.^{19,20} In the United States, perinatal transmission has continued to decrease: As of 2009, 131 cases were reported.²¹ “On average, it takes 17 years to get research directly into practice as the standard of care,” explains Feit. “The HIV/AIDS Bureau has consistently translated advances in the field so quickly; ACTG-076 was a matter of months. Whatever the timeline is, HAB does it faster.”

Over the years, combination ART has optimized outcomes for HIV-positive pregnant women and their infants. The rate of MTCT has dropped to 1 to 2 percent.²² Combination ART also decreases premature births and maternal and infant mortality.²³

Despite the breakthrough in prevention of MTCT, little could be done to prevent HIV progression in people already infected. Although AZT could prolong survival in symptomatic people who had already developed AIDS, it did not entirely halt disease progression, and efficacy waned as a result of drug resistance.^{24,25,26} Starting AZT earlier



A provider at the AIDS Service Center in New York City (seen here) educates a group of consumers. Improved patient literacy is shown to increase medication adherence and retention in care.

did not help. One large study reported that AZT use made no significant difference in rates of disease progression, illness, or death in asymptomatic people with CD4 cell counts below 500 cells/mm³, whereas others found short-term benefits but no ultimate difference in survival.^{27,28,29} “It was frustrating to see AZT work so well [for MTCT] but not for slowing down HIV progression,” recalls Laura Cheever, chief medical officer and deputy associate administrator of HAB.

Researchers were hoping that adding a second drug from the same class (called “dual nucleoside therapy”) would be more effective than single-drug therapy (called “monotherapy”). This approach initially showed promise in people with CD4 cell counts ranging from 200 to 500 cells/mm³. Combining AZT with another nucleoside reverse transcriptase inhibitor (NRTI) slowed disease progression and increased survival;³⁰ however, combining NRTIs in people with AIDS who were pretreated with AZT made no difference in survival.³¹ Ultimately, it became clear that benefits of dual nucleoside therapy were not always durable and that combining two drugs from the same class did not prevent the emergence of drug resistance.^{32,33,34}

Fortunately, advances in technology provided researchers with a new tool: HIV viral load (HIV RNA) testing. Researchers quickly discovered that changes in HIV RNA were predictive of changes in CD4 cell count, so HIV RNA testing could be used for two purposes: to predict disease progression (and, ultimately, risk of death) and to measure response to antiretroviral treatment.³⁵

It was clear that suppressing HIV replication could delay disease progression and prolong survival, but a single class of drugs was insufficient: New weapons in the fight against HIV/AIDS were desperately needed. By 1994, AIDS had become the leading cause of death among people age 25 to 44, and 50,000 people in the United States had died from AIDS-related causes.³⁶

1995: The HAART Era Begins: Preventing HIV Progression

Usually it takes years to get new medical advances out to the people who need it. But we were able to deliver HIV treatment as soon as the protease inhibitors were approved because Ryan White had been funding a system and had already built capacity to deliver multidisciplinary care. It’s not just medical technology; Ryan White put the spotlight on how care is delivered. It’s about culturally competent people that care, providing patient-centered, high quality treatment.

—Laura Cheever,
chief medical officer and deputy associate administrator of HAB

Despite many disappointments, researchers continued to be optimistic about ART; they were hoping that combinations of drugs targeting different steps of the HIV life cycle would be able to stop HIV replication, maintain viral suppression, and allow the immune system to recover.³⁷ Frustration, despair, and rage finally began to give way to hope in late 1995, when saquinavir, an HIV protease inhibitor (PI) and the first drug from a new class, was approved by the U.S. Food and Drug Administration (FDA). In 1996, an HIV viral load test and three new drugs—two PIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI)—were approved by the FDA (see Figure 1, Antiretroviral Drug Approvals by Class and Date). Clinicians finally had what they needed to fight HIV effectively. As Frank explains: “We thought that there was a latency period where nothing was happening with the virus. Finding out that HIV was making billions of copies changed our ideas about clinical management and contributed to the advent of HAART. We found out what the virus was doing, how to measure it, and how to suppress it.”

Hope was replaced by elation in July 1996, at the XI International Conference on AIDS, when David Ho announced that HIV could be eradicated if it was completely suppressed for 2 or 3 years. At the same time, several reports suggested that HIV could be fully suppressed by combining two NRTIs with either an NNRTI or a PI. The HAART

FIGURE 1. ANTIRETROVIRAL DRUG APPROVALS BY CLASS AND DATE¹¹⁰

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

March 19, 1987 Retrovir (AZT; zidovudine) is the first drug approved to treat AIDS	October 9, 1991 Videx (ddI; didanosine) is approved	June 19, 1992 HIVID (ddC; zalcitabine) is approved	June 24, 1994 Zerit (d4T; stavudine) is granted accelerated approval
November 20, 1995 EpiVir (3TC; lamivudine) is granted accelerated approval	December 17, 1998 Ziagen (abacavir) is granted accelerated approval	October 26, 2001 Viread (tenofovir) is granted accelerated approval	July 2, 2003 Emtriva (emtricitabine; FTC) is granted accelerated approval

NRTI Coformulations

September 26, 1997 Combivir (AZT and 3TC) the first coformulated anti-HIV drug, is approved	November 14, 2000 Trizivir (coformulated AZT, 3TC and abacavir) is approved	August 2, 2004 Epzicom (a coformulation of abacavir and lamivudine) is approved	August 2, 2004 Truvada (coformulated tenofovir and emtricitabine) is approved
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Non-Nucleoside Reverse Transcriptase Inhibitors

June 21, 1996 Viramune (nevirapine) is granted accelerated approval	April 4, 1997 Rescriptor (delavirdine) is granted accelerated approval	September 17, 1998 Sustiva (efavirenz) is approved	January 19, 2008 Intelence (etravirine) is granted accelerated approval	May 20, 2011 Endurant (ripilvirine) is approved
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Protease Inhibitors

December 6, 1995 Invirase (saquinavir) is approved accelerated approval	March 1, 1996 Norvir (ritonavir) is approved	March 13, 1996 Indinavir (crixivan) is approved
March 14, 1997 Viracept (nelfinavir) is granted accelerated approval	April 15, 1999 Agenerase (amprenavir) is granted accelerated approval	September 15, 2000 Kaletra (lopinavir and ritonavir coformulation) is approved
June 20, 2003 Reyataz (atazanavir) is approved	June 22, 2005 Aptivus (tipranavir) is granted accelerated approval	June 23, 2006 Prezista (darunavir) is granted accelerated approval

Fusion Inhibitor

Entry Inhibitor

Integrase Inhibitor

March 15, 2003 Fuzeon (T-20; enfuvirtide) is granted accelerated approval	August 6, 2007 Selzentry (maraviroc) is approved	October 12, 2007 Isentress (raltegravir) is granted accelerated approval
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One Pill, Once a Day: Coformulated Regimens

July 12, 2006 Atripla (the first fixed-dose, multiclass, single-tablet HIV regimen) is approved for use in the United States	August 10, 2011 Complera, a fixed-dose, multiclass, single-tablet HIV regimen is approved for use in the United States
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Over the years, many patients have been able to dramatically reduce their pill burden from full medicine cabinets (seen here) to more manageable regimens, and in some cases to just one pill a day.

era had begun. “We had turned directions really quickly. It was like a light switch, going from terrible pessimism to exaggerated optimism in less than a year,” says Cheever.

The dramatic and rapid advances in HIV treatment quickly overwhelmed busy clinicians. Results from clinical trials needed to be translated from the bench to the bedside in the form of treatment guidelines for health care providers, patients, and payers. HHS, the Office of AIDS Research, the National Institutes of Health, the Henry J. Kaiser Family Foundation, and the U.S. Centers for Disease Control and Prevention (CDC) joined forces to provide guidance on the use of ART and guidelines on how to treat HIV with antiretroviral agents. The *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* were issued on April 17, 1998, and the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* were issued on April 24, 1998. The guidelines are updated on an ongoing basis. As of August 2011, the pediatric and adult guidelines have been updated more than a dozen times each. “Lots of information about HIV treatment comes in, all the time, every day. Providers rely on the Department of Health and Human Services guidelines to provide an unbiased synthesis of trial results,” says Cheever.

From the beginning, HRSA staff and Ryan White grantees put science into action and played a crucial role in developing, disseminating, and implementing the HHS guidelines. The Ryan White-funded **AETCs**, are the training arm of the program. “Clinicians got more involved because of what they were seeing. They made themselves experts,” says Steven R. Young, director of HAB’s Division of Training and Technical Assistance. **AETCs** provide local, regional, and national trainings to more than 150,000 clinicians each year, moving advances directly to the community. According to Frank,

AETCs are crucial. They help clinicians keep pace with current research, address disparities in access to care, develop cultural competency, and fight stigma while bringing cutting-edge information right to the community. AETCs build capacity by several means: providing onsite training at clinics, phone consults, bringing clinicians into academic centers for mini-residencies, and offering ongoing consultations for clinicians in rural areas. Many times people have decided to become HIV providers as the result of their work with AETCs. Some people even applied for Ryan White funding and opened an HIV clinic where one did not exist before.

Delivering the Drugs: AIDS Drug Assistance Programs

State AIDS Drug Assistance Programs (ADAPs) are an integral part of the Ryan White HIV/AIDS Program. The first ADAPs began in 1987, when AZT was approved. They were created to ensure that underinsured or uninsured people who did not qualify for government-sponsored health insurance programs would have access to life-saving drugs.

An ADAP volunteer recalls that “people filled out a one-page form to apply, had the doctor sign it and then mailed it, faxed it, or brought it in to the office. We processed applications immediately, so people could go right to the pharmacy and get their medications without worrying about how to pay for them.”

As soon as the treatment guidelines were issued, ADAPs sprang into action. Formularies were expanded to provide the standard of care for treating HIV and preventing opportunistic infections. Program directors began to oversee utilization, and ADAPs developed additional educational materials and programs for medical providers to ensure that clients were receiving appropriate treatment.³⁸ “The CARE Act could roll with the changes,” says Young. “If you look at the last [years of the] 1990s, we ramped up rapidly.”

Although ADAPs have been consistently plagued by funding resource constraints, program directors and staff have worked tirelessly to stretch dollars through coordinating with Medicaid programs, tapping into State high-risk insurance pools to purchase health



Pill boxes like this one are used to assist patients in better managing their antiretroviral medications.

insurance, obtaining rebates from pharmaceutical companies, and using a pharmacy benefits manager to buy and distribute drugs. With growing constraints on State resources, many ADAPs have had to institute cost-cutting measures, such as lowering financial eligibility, reducing the formulary (although they are required to include at least one drug from each class of antiretrovirals), capping enrollment, or instituting waiting lists.^{38,39,40}

Side Effects, Drug Toxicity, and Resistance

Jubilant about HAART began to fade as reports of new side effects, drug toxicity, and drug failure emerged. Reports describing a cluster of metabolic and body shape changes—visible fat loss in the face, limbs, abdomen and buttocks; abnormal fat accumulation in the breasts, abdominal area, and on the back at the base of the neck (“buffalo hump”); elevated lipid levels; and insulin resistance (prediabetes)—in people taking HIV PI-based therapy began to appear.^{41,42} “In the mid- to late 1990s, it was hard to put patients that weren’t really sick on the drugs we had. People had horrible side effects from taking drugs that made feel worse than they did before,” explains Travieso Palow.

The body shape changes had a terrible effect on quality of life; many people felt disfigured by visible signs of HIV infection, and that led to isolation and depression and, in some cases, discontinuation of ART.^{43,44,45,46,47} “I can remember many times we had weekly provider meetings to discuss cases,” says Cheever. “Two years later, no one could believe what we decided to do, because the standard of care changed so rapidly from the early HAART era, when we didn’t even know about toxicities.”

Researchers struggled to discover the cause of metabolic abnormalities and how best to treat them. Eventually, it became clear that certain NRTIs, especially stavudine and AZT, were linked to lipoatrophy.^{48,49} Strategies such as using insulin sensitizers, performing facial reconstructive surgery, and switching antiretroviral agents have been studied, and experts now recommend avoiding stavudine and AZT when other options exist.⁴⁷

In contrast, getting to the cause of and finding treatment for fat accumulation has been more complex. A constellation of risk factors has been identified, such as older age, higher body mass index, lower CD4 cell nadir, and White race.⁵⁰ Several approaches have been studied (e.g., changing antiretroviral agents, diet and exercise, metformin, therapy with testosterone and human growth hormone), and the most effective intervention seems to be treatment with growth hormone analogs.^{47,51,52,53,54}



Doctors review a patient’s chart to check on recent HIV RNA lab results.

Researchers discovered that HIV itself increases the risk for cardiovascular disease, along with certain antiretroviral agents and traditional risk factors.^{55,56} Using certain lipid-lowering agents unlikely to cause significant drug–drug interactions with antiretroviral agents, switching to lipid-friendly regimens, and changing lifestyle (e.g., smoking cessation, aerobic exercise, dietary changes) are recommended to manage lipid abnormalities and to reduce the risk for cardiovascular events.^{57,58} All of these approaches are used by Ryan White providers.

In 1991, the first case of lactic acidosis, a life-threatening condition, was reported in an HIV-positive man who was in a Phase 1 clinical trial of didanosine.⁵⁹ Subsequently, it became clear



A patient listens as his provider explains a new treatment script.

that didanosine, AZT, and stavudine (especially when combined with didanosine) were the culprits.^{60,61} In January 2001, the FDA issued a warning about lactic acidosis and concomitant use of stavudine and didanosine in pregnant and postpartum women and recommended that the combination be avoided unless no other options were available. In February 2002, another life-threatening side effect, ascending neuromuscular weakness, was linked with lactic acidosis related to use of stavudine both alone and in combination with didanosine.⁶²

With HAB guidance, grantees quickly implemented pharmacogenomic testing. Providers could use a genetic test to prevent a potentially deadly side effect and to keep a valuable drug in the armamentarium. Although abacavir was safe and effective for many people, 4 to 5 percent of users suffered from a hypersensitivity reaction (HSR), usually within 9 to 11 days after starting the drug. It was especially concerning that HSR symptoms overlapped with those of common viral infections.⁶³ Researchers made two key discoveries: They found that a genetic variation involved with immune system function, HLA-B57, was associated with HSR and that genetic testing for HLA-B57 could predict abacavir hypersensitivity.^{64,65,66} Once again, science was rapidly integrated into clinical care. The January 2008 guidelines added a recommendation for HLA-B57 screening prior to abacavir use, and AETCs immediately disseminated the recommendation in slide sets and the Spring 2008 *HIV Meds Quarterly Research Brief*.^{67,68}

“We had to talk about side effects and complications of antiretroviral therapy so people knew what to look out for. It was our job to be up on the literature,” says Frank. The severity of these side effects and the urgency of medical interventions required to treat them underscored the importance of rapid information dissemination, a hallmark of the Ryan White HIV/AIDS Program.

Although the benefits of HAART were clearly demonstrated, they came with a price: People had to contend with inconvenient dosing schedules, food requirements, and side effects. Adherence was crucial because skipping doses could lead to drug resistance and, ultimately, to treatment failure.

The recommended approach for treating HIV was to “hit early, and hit hard.” The first HIV treatment guidelines recommended that HIV treatment be started in patients with “<500 CD4+ T cells/mm³ or >10,000 branched DNA or 20,000 reverse transcription polymerase chain reaction copies of HIV RNA/mL” given patient willingness and readiness to initiate treatment.⁶⁹ “We didn’t realize back then that we were developing an environment for people to develop terrible cross-resistance,” says Travieso Palow. “We gave people one new drug at a time, as they came out. We didn’t know any better. Even with the new drugs, people were still dying. We were throwing everything but the kitchen sink at people.”

Unfortunately, clinicians began to notice that HIV drugs were not working for some of their patients. Patients who had been heavily pretreated with NRTIs before PIs and NNRTIs were available had developed drug resistance.^{70,71} Years of trying to keep people alive by treating them with a single drug or by adding new drugs as they came along made it difficult to construct effective regimens, which required at least two active drugs.^{72,73} People were developing resistance to a single drug or even to an entire class of drugs (called “cross-resistance”) after using only one of them.

In 1993, researchers reported that resistance to AZT could be transmitted.⁷⁴ Within a few years, it was clear that resistance to all three classes of antiretroviral drugs could be transmitted, leaving some newly-infected people with limited or no treatment options.^{75,76,77,78}

Once again, technology produced useful tools for guiding HIV treatment decisions: genotypic and phenotypic resistance testing. Genotypic testing could detect mutations in HIV that were associated with drug resistance, whereas phenotypic testing measured the concentration of drug needed to stop HIV from growing. Both tests had limitations: They were expensive, were difficult to interpret, and could miss drug-resistant

According to Travieso Palow, genotypic and phenotypic testing were, in the early days, saved for the worst cases. As of December 2007, however, HHS guidelines recommend genotypic testing upon entering HIV care; when HIV treatment is initiated, when changing HIV medications because of treatment failure; and for pregnant women who have not begun antiretroviral therapy or are on therapy and have detectable HIV.¹¹¹

Treatment Advances and the Ryan White Pharmacist

Ryan White community and clinical pharmacists are an important component of the program and the health care team, helping check for drug-drug interactions and medication errors and assisting with adherence and patient education. To learn more about their involvement, see the [PDF available here](#).

strains unless they comprised more than 20 percent of the virus that happened to be circulating in a person's body when blood was drawn. Initially, use of genotypic and phenotypic testing was recommended in the context of drug failure and for pregnant women, although researchers began to recommend their use for acute HIV and before initiating ART.^{75,78,79,80}

Because results from genotypic and phenotypic testing often required expert analysis, AETCs stepped in with vital resources for Ryan White grantees. They offered onsite trainings, curricula, slides, and fact sheets. The resources incorporated the latest scientific data with guidance for implementing it, including consideration of patient-specific cultural, sociodemographic, cognitive, and psychiatric factors. In California, from 2000 onward, the Positive Health Program at San Francisco General Hospital and the Warmline/National Clinicians' Consultation Center reviewed challenging cases and made treatment recommendations. Case reports from the HIV resistance testing consultation panel are available [online](#).

The first HIV PIs to be brought to market saved countless lives but had some significant limitations, such as side effects, long-term toxicities, drug-drug interactions, and resistance. It was clear that new drugs were needed that were effective against drug-resistant virus and were more tolerable and convenient.

In the meantime, Ryan White grantees maximized the available weapons to fight HIV and AIDS. Having more effective drugs and tests to track disease progression and response to treatment was not enough. Getting these resources to the people who needed them most, by any means possible, was required. Making sure that people were ready to start ART and that they understood how the drugs worked, the possible side effects and strategies for management, and the importance of adherence involved far more than having a brief conversation or handing someone a brochure. It meant meeting people where they were. "Ryan White brought a different, more comprehensive patient- and family-focused model," says Aranda-Naranjo. "Many of the women we were serving had been living in poverty before HIV hit them. Employment, housing, and domestic violence were major issues. We saw the whole person, not just the biological aspect. If people didn't come to our clinic, we went to them," she explains.

Hurricane Katrina and Ryan White

More than 20,000 HIV-positive people were evacuated from areas affected by Hurricane Katrina. HRSA encouraged programs to waive their usual eligibility criteria, including the need for medical records, so that evacuees did not have to interrupt their HIV treatment. Within a month, 1,500 evacuees had been served by Ryan White providers in other States.

Louisiana's ADAP staff was forced to relocate; nonetheless, they immediately began to look for their clients. Texas' ADAP worked with pharmaceutical companies and Louisiana's Medicaid program to provide uninterrupted treatment to all evacuees. In Alabama, grantees reached out to the State department of health, community-based organizations, AIDS service organizations, and private philanthropic organizations for help, and they were able to reopen clinics after only a week. Louisiana's grantees kept working to provide services despite damaged facilities, loss of equipment, and staff shortages. In Mississippi, grantees from destroyed sites worked from trailers.⁸¹

HRSA staff and Ryan White grantees contributed to the development of resources to help providers deliver care after catastrophic events. *Recommendations for Non-HIV-Specialized Providers Caring for Displaced HIV-Infected Residents from the Hurricane Disasters* were issued less than a month after Katrina hit, and by 2008, the *ADAP Emergency Preparedness Guide* was released. Since Hurricane Katrina, HRSA has held many trainings on the topic of emergency preparedness, including presentations at the biennial All-Grantee Meeting.

Did You Know?

Part E of the Ryan White HIV/AIDS Program gives the Secretary of HHS the authority to use up to 5 percent of supplemental funds appropriated under Parts A and B for addressing the needs of public health emergencies, such as aiding people requiring HIV/AIDS care and treatment in disaster areas.

Salvage

Researchers and clinicians tried several strategies to treat people with multidrug resistance. Strategies included increasing drug levels by adding a pharmacokinetic booster; interrupting treatment, in the hope that drug-sensitive virus would rebound; initiating multidrug rescue therapy (mega-HAART), which entailed as many as nine drugs, some recycled from previous regimens; and using genotypic and phenotypic resistance testing to identify drugs likely to work.^{82,83,84,85}

Ultimately, mega-HAART and treatment interruptions were discarded because of their inefficacy, drug toxicity, and availability of new and more potent drugs.^{86,87} Enfuvirtide, an injectable fusion inhibitor, was the first drug from a new class to be approved in 6 years. It provided a bridge for many people that allowed them to survive until better options were available. By 2007, several new medications were available, including drugs from novel classes (an integrase and an entry inhibitor) and second-generation PIs active against drug-resistant virus. These drugs offered hope to people who had been without treatment options, although, as Feit cautions, “There is still no treatment that is as good as not being infected.”

Getting Smart

The value of HIV treatment was underscored by results from the Strategic Management of Antiretroviral Therapy (SMART) study. SMART compared continuous HIV treatment to intermittent therapy (guided by CD4 cell count). The study was stopped early because the results were overwhelming: Illness and death from both AIDS-related and non-AIDS-related causes were significantly higher in the intermittent therapy group than those who remained on continuous therapy.⁸⁸ When researchers looked more closely at data from SMART, they observed that death rates were linked with higher levels of inflammation markers in the bloodstream and that these markers were present at higher levels in people on intermittent treatment than in those on continuous therapy.⁸⁹

The push was to get people onto HIV treatment earlier, but treating HIV was not enough. PLWHA were getting older and were developing conditions traditionally related to aging, such as cardiovascular disease, frailty, renal and hepatic failure, and non-AIDS-related cancers, decades before their HIV-negative counterparts. People with higher CD4 cell counts are more vulnerable to non-AIDS-related death, although mortality from those conditions has increased among all HIV-positive people.^{90,91}

Although HAART as well as access to care and treatment had drastically reduced AIDS-related death rates in the United States, not everyone was reaping the benefits of HIV treatment. Death rates remained higher among injection drug users, and people with HIV were now surviving long enough to die from other comorbid, non-AIDS-related conditions, such as hepatitis C virus (HCV), diabetes, and pulmonary disease.^{92,93,94} “It’s like night and day. . . . In the 1980s, when we were seeing AIDS in hospital inpatient units, the time from diagnosis to death was 3 to 6 months; now it’s more than 25 years, an unbelievable increase in longevity. Now we need to consider all the chronic diseases that pop up longitudinally,” says Young.



Because of treatment advances, HIV primary care doctors are now addressing all the health related conditions associated with old age.



In the early years of the epidemic, before HAART, it was not uncommon for patients to take a plethora of medications to treat their HIV—something that posed very real barriers to adherence.

Providers now need to focus on all-around primary health care in addition to management of HIV disease, particularly as the population of people who are aging with HIV has grown. In 2009, according to the CDC, 28 percent of people living with HIV were older than age 50.⁹⁵ By 2015, one-half of the HIV-positive population in the United States will be older than 50 years of age.^{95,96} Older PLWHA are likely to suffer from other comorbidities; long-term toxicity from ART; and complications from HIV itself, including cognitive impairment, frailty, bone loss, renal, hepatic and cardiovascular disease, type 2 diabetes, high cholesterol, and hypertension.^{97,98}

Polypharmacy (use of several prescription medications at the same time) is common among older PLWHA. One study found an increasing number of medications prescribed to PLWHA as they aged, from an average of more than 7 drugs for people in their 20s to more than 12 medications for people in their 50s and more than 14 drugs for people in their 60s.⁹⁹ Many drug-drug interactions occur between antiretroviral agents and medications for common comorbid conditions (e.g., PIs and certain drugs used to lower cholesterol). A significant amount of research has been devoted to identifying and managing or avoiding drug-drug interactions. Providers have many resources available to guide successful comanagement of HIV and other conditions and to avoid drug-drug interactions. AETCs have produced a variety of materials, including charts, tables and posters, pocket guides, slide sets, and links to online databases.

HRSA's Ryan White HIV/AIDS Program has evolved in response to a changing epidemic. A deadly disease has turned into a treatable condition. "If someone is going to die in 6 months, closure with family and friends matters most," says Cheever, "but when they are going to live for at least 20 years, getting off heroin is important. There are very few medical interventions that have made as much difference as ART. It allows us to address multiple priorities and improve outcomes."

The Ryan White HIV/AIDS Treatment Modernization Act of 2006 reflected this change. For the first time, 75 percent of funds had to be dedicated to 13 core medical services. Support services needed to be essential to delivery of HIV medical care. The focus included getting more people into care, as early as possible, and keeping them there. "Ryan White has quickly adapted to change. It's more than prescribing a new drug,

Getting in Care, Getting Treatment

“Retention in care is linked with better overall health and survival among people with HIV/AIDS [including treatment adherence]. Ryan White uses quality improvement measures, and system level measures such as the number of people with AIDS who get to their first and second appointments because the second visit has been shown to be an indicator of retention in care—the “no-show” rate drops dramatically among people who make it to their second medical visit. Many Ryan White-funded programs now have concierge services. At their first visit, people are introduced to staff who will call them to follow-up. They can work with patient navigators and get linked to care and a second appointment.”

—Laura Cheever,
Chief medical officer
and deputy associate

it’s a philosophical shift from deadly to chronic,” says Cheever. “We didn’t worry about people quitting smoking or getting a colonoscopy. Now we can.”

Getting Better All the Time

On October 12, 2009, a few days after it passed the Senate, the House of Representatives passed the Ryan White HIV/AIDS Treatment Extension Act of 2009 by a vote of 408 to 9, and President Obama signed it into law October 30, 2009.

Ryan White grantees continue to grow with the epidemic. Because the medical tools to treat HIV are available, it has become increasingly important to reach the people who need them, to get those people into care, and to make sure that they remain engaged. In fact, a key provision of the 2009 reauthorization involves bringing people, especially members of poor, minority, and underserved populations who are unaware of their status, into care and maintaining them in treatment.

The [Special Projects of National Significance \(SPNS\) program](#) looks at innovative ways to deliver HIV care and treatment where it matters most. [SPNS models](#) are designed and intended for implementation by Ryan White grantees. “SPNS can shift models of care . . . HIV is a chronic illness—we need to deal with the things that are killing people,” says Cheever.

Trio of SPNS

The [Hepatitis C Treatment Expansion Initiative](#) is looking at best practices for delivering HCV treatment to people coinfecting with HIV. HCV is highly prevalent among people with HIV: In the United States, as many as 30 percent of PLWHA are coinfecting.¹⁰⁰ End-stage liver disease from HCV is now a leading cause of death among PLWHA. Several new HCV drugs are in development and are being or will be studied in HIV/HCV coinfecting people, so it is more important than ever to optimize delivery of HCV treatment.¹⁰¹

SPNS focuses on where the need is greatest. From the beginning of the epidemic, HIV/AIDS has had a devastating and disproportionate impact on African-American and Hispanic/Latina women. In 2010, the CDC estimated that 1 in 30 African-American women and 1 in 106 Hispanic/Latina women will contract HIV.^{102,103} Minority women have traditionally been underrepresented in clinical trials; often suffer from comorbidities such as depression and substance use disorders; are often uninsured; and have worse outcomes across a range of conditions, including HIV/AIDS.^{104,105} The [Enhancing Access to and Retention in Quality HIV/AIDS Care for Women of Color Initiative](#) will identify innovative methods of reaching and continuing to deliver care to women of color and getting them into treatment.

HRSA has worked diligently to ensure that advances in HIV treatment will benefit people who need them most, not just those who are easiest to reach. Because HIV/AIDS is prevalent among current and former drug users, treatment for substance use disorders is one of the core medical services specified in the Ryan White HIV/AIDS Treatment Extension Act of 2009. According to the CDC, more than one-third of AIDS cases and 19 percent of HIV cases are attributed to injection drug use, and survival is poorer among PLWHA who are injection drug users, in part because of late initiation of ART.^{106,107,108,109}

In late 2002, the approval of buprenorphine for treatment of opioid dependence marked a significant advance in the field. In 2004, HRSA launched the [Buprenorphine Initiative: An Evaluation of Innovative Methods for Integrating Buprenorphine Opioid Abuse Treatment in HIV Primary Care](#). This initiative reflects the ongoing commitment of Ryan White staff and grantees to optimize delivery of care to PLWHA. The buprenorphine initiative evaluated feasibility and effectiveness of integrating medication-assisted treatment for opioid dependence into HIV primary care. For more information about HIV primary care and buprenorphine, see the [HRSA CAREAction](#) newsletter on medication-assisted treatment, available online (<http://hab.hrsa.gov/newspublications/careaction-newsletter/may2011.pdf>); and look for the forthcoming buprenorphine monograph.)



To avoid medication errors and assist with adherence, many providers use pictorials of antiretroviral medications. This is particularly helpful for those with low health literacy.

Conclusion

The quality of my health care is based on the fact that the Federal Government is involved. Without the force of the HHS guidelines and the HIV/AIDS Bureau performance measures, people like me wouldn't be doing what I do today. I was diagnosed with HIV in 1987 and got my AIDS diagnosis in 1995.

—Brian Feit,
public health analyst in HAB's Technical Assistance Branch and HRSA's
National HIV/AIDS Training and Technical Assistance Program

Ryan White grantees can now demonstrate that their patients are getting optimal care and treatment by using tangible measures selected according to the needs of the populations they serve. Measures include core clinical items relevant to the health outcomes of PLWHA (e.g., antiretroviral use, CD4 cell count; PCP prophylaxis; screenings for tuberculosis, hepatitis B and C, and syphilis; influenza vaccines; screenings for substance use and mental health) as well as oral health, pediatrics, medical case management, and systems-level measures, such as waiting time for access to care and disease stage at entry into care.

It is clear that Ryan White grantees are continuing to step up to the challenge of a dynamic epidemic that has transformed their role from administering palliative care to providing comprehensive health care in a culturally competent, patient-centered, multi-disciplinary medical home. “We provide for the needs of infants, children, and the families that love and care for them in a welcoming environment,” says Cheever. “Given the complex nature of HIV—how it intersects with stigma and health disparities—you need to treat the whole patient. If you can get people into care with providers who know what they are doing, and support, case management, food and transportation are provided, you will have a good outcome.”

For more than two decades, the Ryan White HIV/AIDS Program has brought scientific advances to people who need it most: the poor and the underserved. Grantees have taken the lead in implementing new data, and they have successfully translated scientific progress into life-saving clinical practice.

Ryan White grantees have demonstrated the capacity to adapt rapidly. The system can adjust rapidly to changing circumstances and is staffed by a remarkable people. In coming years, grantees face the challenges of serving an aging population; finding undiagnosed persons, bringing them into care, and retaining them; and implementing recent advances in HIV prevention, all in the context of a shifting health care system.

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