

Treatment

AIDS Drug Assistance Programs: A Lifeline for People with HIV

By Murray Penner and Jen Kates

More than twenty years after the approval of the first antiretroviral and despite numerous advancements in the treatment of HIV, getting HIV-related medications to all those who need them remains a critical challenge, even in the United States. Throughout this time, ADAPs, or AIDS Drug Assistance Programs, have served as the medication lifeline for many people with HIV.

What are ADAPs? Part of the Ryan White HIV/AIDS Treatment Modernization Act of

insurance (premiums, co-payments and deductibles) that includes coverage of HIV treatments.

When Did They Begin? ADAPs began in 1987 as AZT Assistance Programs when the federal government provided grants to states to help them purchase the first FDA-approved antiretroviral, AZT, for people living with HIV/AIDS. As community members began demanding that treatment be accessible and that the federal govern-

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2006 (Ryan White Program), ADAPs are the major source of prescription drugs for low-income people living with HIV/AIDS in the U.S. who have limited or no prescription drug coverage. The purpose of ADAPs, as stated in the Ryan White law, is to “provide therapeutics to treat HIV disease or prevent the serious deterioration of health arising from HIV disease in eligible individuals, including measures for the prevention and treatment of opportunistic infections”.¹ This is accomplished in two main ways—providing Food and Drug Administration (FDA)-approved HIV-related prescription drugs to people living with HIV/AIDS and paying for health

ment develop a response to the HIV/AIDS crisis, ADAPs were written into the newly created Ryan White CARE Act in 1990; in 1996, the Congress began earmarking funds for ADAPs specifically, as part of Ryan White. In that year, approximately 69,000 people were served by ADAPs.² Today, close to 150,000 people are served.

How Do They Work? Each state³ administers its own ADAP and is given flexibility under the Ryan White Program to design many aspects of the program, including client eligibility, drug purchasing and distribution arrangements, and drug formularies (although there are mini-

num requirements for including one drug from every class of antiretroviral medications). No standard client income eligibility level is required by law, although clients must be HIV-positive, low income and under- or uninsured. In June 2007, client eligibility levels ranged from 200% of the federal poverty level (FPL) in nine states to 500% FPL in six states. Twenty-five states had levels over 300% and 19 states had set their levels between 201% and 300% of the FPL (see Figure 1). The national ADAP budget in Fiscal Year 2007 was \$1.43 billion. Major sources of revenue were federal funding through the Ryan White Program (54%), state general revenue funds (21%) and drug rebates from manufacturers (18%).⁴

ADAPs serve as “payer of last resort”; that is, they provide prescription medications to, or pay for health insurance premiums or maintenance for, people with HIV/AIDS when no other funding source is available to do so. Demand for ADAPs depends on the number of clients seeking services, the cost of medications, and the size of the prescription drug “gap” that ADAPs must fill in their jurisdiction. Larger gaps, such as in states with a less generous Medicaid program, may strain ADAP resources further than in others. This, coupled with an estimated annual (2007) drug cost for each ADAP client of nearly \$12,000 and escalating prescription drug costs, places ADAPs under continual fiscal pressure to meet the demands for services.⁵

ADAPs are discretionary grant programs, dependent on annual funding from Congress, funding which may not correspond to the number of people who need prescription drugs. Therefore, annual federal appropriations and contributions from other sources (such as state funding), determine how many clients ADAPs can serve and the level of services they can provide. When demand for ADAPs exceeds available funding, as has been the case for much of the program, ADAPs have turned to a variety of cost containment measures, including waiting lists, reduced formularies or client eligibility, cost-sharing and/or expenditure limits (monthly or annual). Waiting lists, while not the only indicator of fiscal pressures within ADAPs, have been a steady element of ADAPs since 2002 when tracking began. The number of individuals on ADAP waiting lists reached a high

of 1,629 in 11 states in 2004, and has fluctuated over time, most likely a result of variable funding levels and demand for services.⁶

What are the Latest Program Trends? Through a more than 10-year collaborative effort, the National Alliance of State and Territorial AIDS Directors (NASTAD) and the Henry J. Kaiser Family Foundation (Kaiser) have been working to

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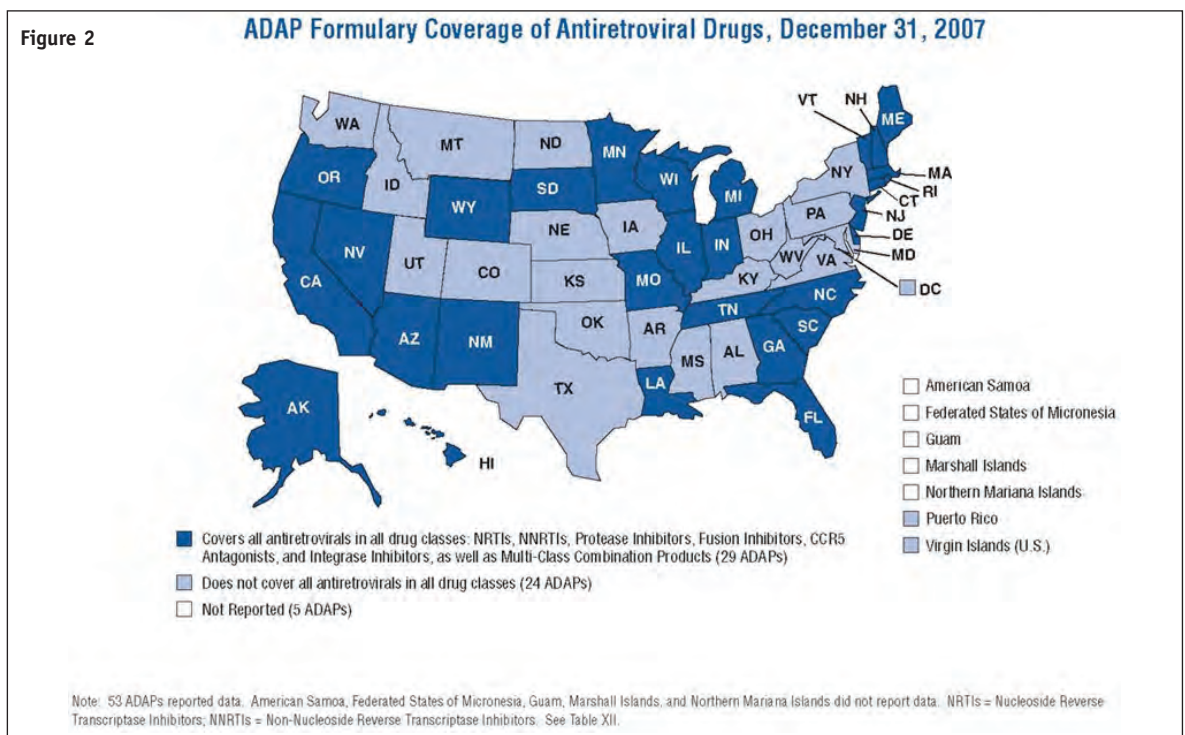
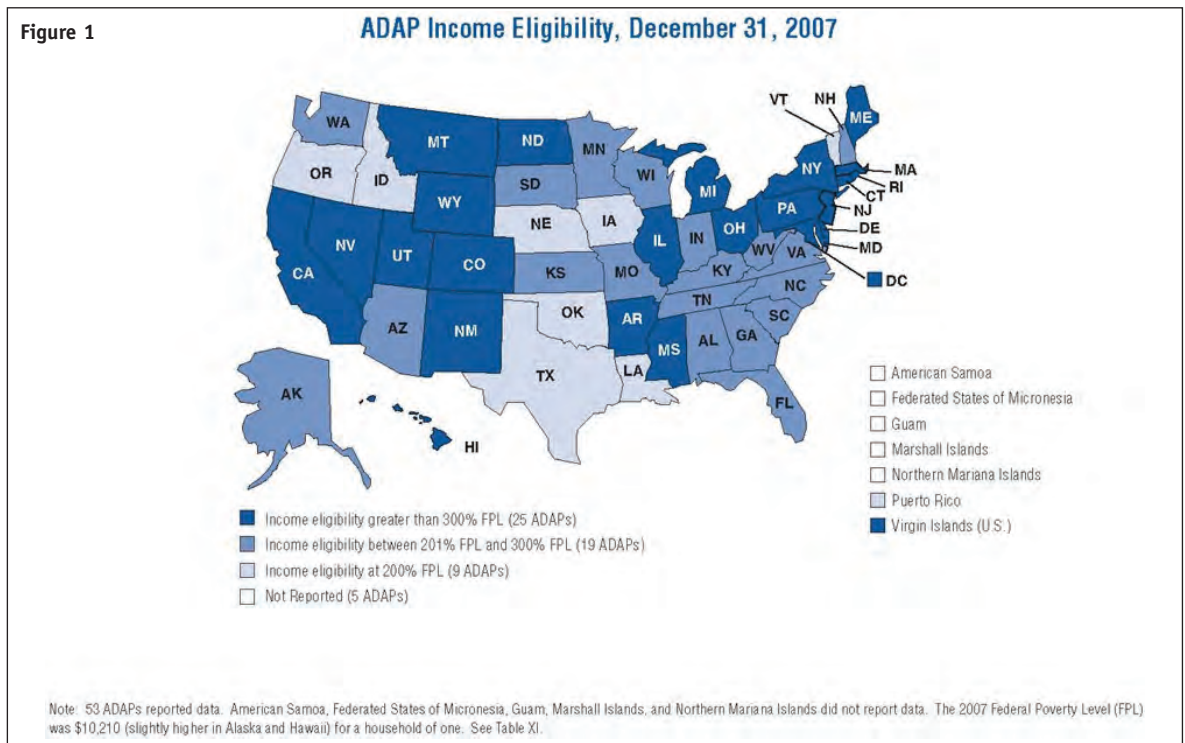
collect data on ADAPs through The National ADAP Monitoring Project, which tracks the program on an annual basis. The most recent report, from April 2008, highlighted several key findings about ADAPs, including the following:⁷

- **Across the nation, ADAPs have served an increasing number of clients over time.** With nearly 146,000 enrollees in 2007—and 102,000 served in the month of June 2007 alone—the national ADAP client caseload was at its highest level since the program began. It is estimated that ADAPs reach nearly three in 10 people with HIV estimated to be in care nationally.⁸
- **As the nation’s prescription drug safety-net for people with HIV/AIDS, ADAPs are designed to serve some of the most vulnerable people with HIV in the country, and, indeed, most clients are low-income and uninsured, with more than four in 10 having incomes at or below 100% of the Federal Poverty Level (FPL was \$10,210 annually for a family of one in 2007), and seven in 10 being uninsured.** Approximately two-thirds are people of color. Without ADAPs, many of these individuals would likely fall through the cracks in the larger health care system.
- **ADAP clients primarily reflect the national epidemic, concentrated in states with the highest incidence of people living with HIV/AIDS.** Ten states accounted for two-thirds (67%) of total client enrollment in June 2007. Regionally, more than a third (37%) of clients enrolled lived in the South, 27% in the

West, 25% in the Northeast, and 11% in the Midwest.

- The 2006 reauthorization of the Ryan White Program, the federal program under which ADAPs were established, changed the

way in which federal funding is distributed to states for ADAPs. It also instituted new ADAP policies such as a minimum drug formulary requirement for antiretrovirals, the first such requirement in the program's history.



Source: Kaiser Family Foundation and NASTAD, *National ADAP Monitoring Project—Annual Report, 2008*

While the implications of these recent changes are still playing out at the state level, they have introduced both new opportunities and new challenges for ADAPs. For example, the funding formula change has resulted in fluctuations in the amount of ADAP funding received by states between Fiscal Year 2006 and Fiscal Year 2007 and may continue to do so. Additionally, the new formulary requirement has served to expand access to medications in a few states but may pose resource challenges in others, particularly as newer, but usually more expensive, classes of antiretrovirals are introduced (see Figure 2).

- There generally has been good news for ADAPs, as several factors have combined to ease past fiscal pressures, although relief has not been felt equally across the country and its longevity is uncertain. Waiting lists are at nearly their lowest levels since the Monitoring Project began tracking them: as of July 3, 2008, there were 35 individuals on ADAP waiting lists in two states (Indiana and Montana). Over the past year, most ADAPs increased client enrollment and added medications from two new drug classes (integrase and CCR5 inhibitors) almost immediately upon their approval, despite having a multi-month grace period for doing so.

Among the factors contributing to the easing of past pressures for many states were:

- *President's ADAP Initiative (PAI)*: The PAI, initiated in 2004, provided additional one-time funding to 10 states with waiting lists, resulting in a drop in the number of people on waiting lists throughout the country (although not eliminating waiting lists completely; at the end of the PAI in 2006, more than 300 additional individuals were still on waiting lists in six states).
- *Medicare Part D*: Some ADAPs reported that the introduction of Medicare Part D in 2006 helped to ease constraints and/or provide a new avenue for prescription drugs for people with HIV. For example, many ADAPs have been able to reduce drug costs for Part D-eligible clients by transitioning from paying all prescription drug costs for Part D-eligible clients to covering their wrap-around

costs such as co-payments, monthly premiums or costs when beneficiaries reach the coverage gap in their Part D plans.

- *Non-Federal Funding Sources*: Over time, non-federal funding sources-particularly state general revenue support and drug rebates-have become critical parts of the ADAP budget. States, although not required to do so, have generally acted to provide additional funding to ADAPs at

Annual federal funding determines how many clients ADAPs can serve.

key times, sometimes in response to state-level advocacy efforts. In addition, the easing of the economic downturn that hit states hard in the early part of the decade likely led to some states increasing their contributions to ADAP this year. Moreover, because of the uncertainty of ADAP funding from year to year, ADAPs have become increasingly sophisticated at seeking other sources of revenue, particularly pharmaceutical manufacturer drug rebates, which now appear to be a main factor allowing most ADAPs to continue to meet client demand and even expand access in some cases.

- *ADAP Supplemental Treatment Drug Grants*: The 2006 Ryan White reauthorization increased the amount of funding available for ADAP Supplemental Drug Treatment Grants, a set-aside of the federal ADAP earmark designed to provide additional funding to states with significant ADAP program limitations. This resulted in the first increase in funds available through the ADAP Supplemental since Fiscal Year 2003 and likely contributed to the easing of fiscal pressures in those states that received increases in (13 states) or first-time (3 states) ADAP Supplemental funding.
- **Despite these factors, there is concern for the future of ADAPs.** ADAP funding levels and budget compositions are highly variable from year to year, with revenue sources often

triggered as “levers” that rise and fall depending on the amount of federal funding available. Trend data indicate that when one revenue source decreases, others often increase to fill the gap. For example, as growth in federal ADAP earmark funding has slowed in recent years, other funding sources, such as drug rebates, have been sought more actively. These “levers”, however, are seldom permanent and usually unpredictable. The only two ADAP funding sources that increased over the last period were drug rebates and the ADAP Supplemental; all others decreased, including state funding, which has historically been a key driver of ADAP budget growth

The Outlook? As of the time of this writing, there are still several unknowns concerning the near and longer term outlook for ADAPs. It is still not clear, for example, how the recent changes in the Ryan White Program will affect ADAPs over time. ADAP earmark funding, for instance, is still expected to shift state-by-state as hold harmless requirements (provisions within the Ryan White law that protect jurisdictions from substantial losses in funding) and other provisions in the law play out. This is occurring against the larger backdrop of a more general economic downturn that is impacting state budgets, with many reporting overall budget shortfalls for Fiscal Year 2008 and/or expecting shortfalls for Fiscal Year 2009, which could stand to affect ADAPs.

Both presumptive Presidential nominees have mentioned the need to address the growing HIV epidemic in the U.S.

In addition, Fiscal Year 2009 Congressional appropriations for ADAP have still not been completed by Congress. Both the House and Senate have proposed increases of approximately three percent over current levels, but differences between them must now be resolved. The pending national election could bring changes as well, with both presumptive Presidential nominees having mentioned the need to further address the growing HIV epidemic in the U.S. Furthermore,

there is ongoing discussion nationally and at the state level about the need for broader health reform, and any changes in the larger health system will stand to affect ADAPs. What is clear is that ADAPs have and will continue to play a critical role in providing prescription medications to people with HIV/AIDS in the U.S. who would otherwise have nowhere else to go.

ADAPs have been highly successful in meeting the needs of uninsured and underinsured Americans with HIV. As the new President, Congress and states seek to affect changes in health care, the role of ADAP as a safety net program in our nation’s larger health care system remains critical and must be at the forefront of health care reform discussions.

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- 3 The term “state” is used to include states, territories, and associated jurisdictions.
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The Coming Crisis

By Paul Dalton

The last few years have witnessed remarkable progress in treating people with advanced and drug-resistant strains of HIV. Four powerful drugs became available that either overcame drug resistance (Prezista [darunavir, TMC-114],

Intelence [etravirine, TMC-125]) or were from entirely new classes [Selzentry (maraviroc), Isentress (raltegravir)].

This marked an important and unique moment in HIV drug development. Never before had so many new and effective drugs emerged in such proximity. People with extensive experience taking HIV drugs have been able to put together powerful regimens with two or more fully active agents—often for the first time.

The tremendous promise of these new drugs represented an exciting moment, but emphasis needed to be placed on using them carefully and correctly, while also noting that this moment was unlikely to recur. The message was clear: “Seize this opportunity, use the new drugs carefully, and don’t waste this once-in-a-lifetime chance.”

As good as some of these newer drugs have looked in studies, there are emerging signs of trouble. Dr. Steven Deeks, a prominent HIV physician and researcher says, “Although the current generation of drugs are generally doing great, many patients are not responding in a durable manner. We are now following about 25 individuals who have failed all six drug classes. The key now is to design regimens to maintain immunologic and clinical stability while we wait for more drugs. I am concerned, however, as it will likely be a few years before we have another shot at getting the virus under control. We desperately need a second generation integrase inhibitor that works against viruses resistant to raltegravir.”¹

Dr. Deeks’ experience is far from typical. He follows many of the most treatment experienced people in the San Francisco Bay Area, many of whom have been on therapy since 1987. Although not typical, his experiences have been reported elsewhere, if in smaller numbers.

Nonetheless, this suggests a burgeoning problem of people beginning to run out of treatment options, as has happened a couple of times during the epidemic. Some are concerned that the most vulnerable people living with HIV will be left with few or no viable treatment options, possibly for many years.

One of the unintended effects of the recent successes in drug development is that fewer people are available for studies of experimental drugs aimed at treatment experienced folks. We saw this coming and have been counseling drug companies

and the Food and Drug Administration (FDA) that the era of ‘TORO-like’ studies was coming to a close. These studies give volunteers optimized background therapy (the best combination of HIV drugs chosen with resistance test results) with either the experimental drug or a placebo. The design allows regulators, scientists and activists to clearly see the benefit of the new drug. Some call

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these studies ‘TORO-like’ after those that led to the approval of Fuzeon [enfuvirtide, T20].²

This contrasts with how studies of first line treatment are done.³ When studying HIV drugs as first line, the basic model is head-to-head non-inferiority studies,⁴ which are designed to tease out the relative contribution of entire regimens rather than the individual drugs.

The FDA has allowed non-inferiority studies for drugs being studied as first line, but has insisted on placebo controlled superiority studies for treatment experienced studies. Treatment experienced patients have been exposed to prior HIV treatment regimens. The current process made a good deal of sense when there were many people signing up for these studies, but the situation is now quite different.

While there are not enough people signing up for these kinds of studies, there is still a sizeable need for studying new HIV drugs. This, combined with the thin drug pipeline and the current difficulty recruiting for studies, may add up to real trouble down the line.

In meetings with every drug company working in HIV, Project Inform has warned of this impending problem and recommended adopting new ways of studying their drugs. The reaction has been mixed. While some companies have been quite open to new ideas, it is fair to say that most would prefer to stick with models that, until now, have proven successful.

We have struggled to argue—to the companies and the FDA—that new ways of studying and developing drugs are both necessary and possible. It would take some creative thinking on the

part of the companies and their scientists, along with open mindedness and flexibility on the part of the FDA.

Gilead Sciences is one of the first to grapple with this. When it came time to do large, pivotal studies of their experimental integrase inhibitor, elvitegravir, there were not enough participants in the US to initiate a typical study of treatment experienced patients. Project Inform had warned Gilead and others of this eventuality and argued for studies that would more closely resemble the head-to-head, non-inferiority studies used for studying first-line drugs.

At first, Gilead thought they could follow the old, tried and true development plan. They explored performing a TORO-like study for elvitegravir, fully believing that it gave them the best chance at moving their drug ahead.

Over time Gilead came to see that a new plan was needed to move forward. They submitted a plan to the FDA that closely resembled the type of study for which many had been advocating.

The FDA eventually allowed Gilead to move forward with this study design for elvitegravir. There was great concern that they wouldn't, as it took longer than usual for the FDA to make a decision on Gilead's phase III trial proposal.

This is a great victory for people living with HIV. Both the company and the FDA came around to see that new thinking was required to respond to a new environment. With this new sit-

uation, there is a great need for new treatments to be developed and for the FDA and companies to think and act creatively to ensure this happens.

are either cutting back or eliminating their drug development plans. The marketplace for HIV drugs is both crowded and competitive. The scientific hurdles for developing new HIV drugs have also grown more difficult, making it a less attractive market for companies.

While there are real challenges facing the industry at this time, it is a mistake to think either that HIV is largely a solved problem, or that there isn't room for new drugs. While it is true that drugs have improved and most people are able to get good, durable responses from their drug combinations, there is plenty of room for improvement. HIV is largely a data driven market, and good drugs will always find their way into wide use.

The Food and Drug Administration (FDA)

The FDA is responsible for ensuring that drugs are safe and effective before they become available outside clinical studies, as well as when they are on the market. Recent media stories that focused on drug safety, particularly on Vioxx and Heparin, have created a somewhat fearful climate inside the FDA where new ideas are met skeptically. Their recent decision to green light elvitegravir's development shows that at least its antiviral division is open to creative drug development plans.

The FDA must strive to find a balance between protecting the safety of health care consumers while not unduly discouraging drug development. While it isn't always easy, the FDA has been largely successful when it comes to HIV.

The Current Drug Pipeline

All in all, the pipeline is both thin and unimpressive. There are a few "me too" drugs (slight changes in existing drugs) which are helpful but not game-changing. A few novel compounds may prove promising down the line, but they are struggling right now, due to either study results, or in one case, the company is being bought by a company that does not want to work in HIV.

As for those drugs in human studies, the closest to approval is rilpivarin (TMC-278), a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) for first-line treatment being studied against Sustiva.⁵ Sustiva has gone largely unchallenged as a first line NNRTI, but its neuro-psychological side effects make it difficult for many people to take. A new, potent first-line NNRTI

The most vulnerable people living with HIV will be left with few or no viable treatment options, possibly for many years.

The Current State of HIV Drug Development

The Industry

As a whole, the pharmaceutical industry has done a tremendous job developing HIV drugs. However, many signs are showing a fading commitment to HIV. Fewer new companies are getting into HIV, and some well established ones

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that is free of such side effects could be a great advance for people with HIV. Also of note, rilpivarin is an ideal candidate for co-formulation, which would allow it to combine with another drug in a single dosage form. Thus, not only could it be competitive against Sustiva, but Atripla might be seeing some real competition too.

Vicriviroc, Schering's CCR5 drug, continues to flounder but is still viable.⁶ Bevirimat, a maturation inhibitor from Panacos, has been hamstrung by formulation problems, which we understand have been overcome. Other promising drugs are Pharmasset's racivir, and Avexa's apricitabine.

The lack of excitement with the current pipeline offers a real opportunity for both new and established companies to make a real move in to HIV. There is a demonstrated need for improved versions of existing drugs and, more importantly, new types of drugs. The greatest needs right now are second generation Integrase Inhibitors, CCR5 antagonists, unboosted protease inhibitors and novel targets.

The Bottom Line

The past two years have been a boon to people with extensive treatment experience. Four successful

new drugs, including two new classes, have meant most people can put together powerful, effective and tolerable regimens, even if they've never been able to get to undetectable before. However, this period is now over, and we're experiencing a major downturn in the number of promising drugs in the pipeline.

This reinforces the importance of using the current crop of new drugs correctly. Your best chance at getting to and staying undetectable is to start a regimen with at least two and hopefully three fully active drugs. If you are able to do this and get your HIV level to undetectable, good adherence is the best way of keeping it there.

This also points to the need for treatment activists to continue to work with the companies, scientists and regulators to ensure that new drugs are developed.

Lastly, this situation points toward the need for a cure. It is only going to become more difficult to keep the companies, their researchers and the general public interested in HIV drugs. There is a growing sense that HIV is not that much of a problem anymore, at least not in wealthy countries.

The only real solution is a cure. Many promising approaches are under study, as well as resurgence in community activism aimed at cure research. A conscientious program mounted by academia, industry, government and community is necessary to reach this goal.

Paul Dalton is Director of Treatment Information and Advocacy at Project Inform.

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1 Integrase inhibitors, such as raltegravir are a class of antiretroviral drug that block the action of integrase, an enzyme that integrates genetic material from the virus into its target cell.

2 Fuzeon is in a class of antiretroviral drugs, fusion inhibitors, which are used in combination therapy for the treatment of HIV. Fusion inhibitors interfere with the binding, fusion and entry of HIV to a human cell. By blocking this step in HIV's replication cycle, fusion inhibitors work to slow the progression from HIV infection to AIDS.

3 A first-line treatment is a medical therapy recommended for the initial treatment of a disease, such as HIV.

4 Non-inferiority means that one drug or regimen is equivalent or nearly equivalent to another.

5 NNRTIs inhibit the activity of reverse transcriptase, a viral DNA polymerase enzyme that HIV needs to reproduce.

6 CCR5 is a protein expressed on the surface of cells, including T-cells, that is most commonly targeted by the virus.