13th CROI surprise: Antiretrovirals are good for you
13th CROI surprise: Antiretrovirals are good for you

Mark Mascolini

With a flourish of studies on structured treatment interruptions and the cardiovascular complications of HIV infection and its therapies, IAPAC Monthly Writer-At-Large Mark Mascolini predicts the 13th Conference on Retroviruses and Opportunistic Infections may prove a turning point in the management of this pernicious disease.
Poor adherence to the treatment of chronic diseases is a worldwide problem of striking magnitude. According to the World Health Organization (WHO), adherence to long-term therapy for chronic diseases in developed world countries averages 50%. These rates are assumed to be even lower in developing world countries given poor health literacy and scarcities in health care delivery systems.

Because the consequences of poor adherence to long-term therapies are poor health outcomes and increased health care costs, there is a need to examine strategies through which to improve adherence through processes that are multidisciplinary in approach and continuous in scope. The time for intervention is now, because the impact of poor adherence grows as the burden of chronic diseases grows. Non-communicable diseases and mental disorders, HIV disease, and tuberculosis combined represented 54% of the worldwide disease burden in 2001, and may exceed 65% worldwide in 2020.

With respect to HIV/AIDS, a review of 15 US National Institutes of Health (NIH)-funded studies conducted between 1997 and 2005 reveals widely varying levels of adherence to antiretroviral therapy among more than 2,800 patients involved in the 15 cohorts—from 53% to 90%. Because adherence to antiretroviral therapy is a determining factor in its short- and long-term success, it must come to the forefront of our thinking as antiretroviral therapy is scaled up in developing countries, and as patients in developed countries continue to age with.

Continued on page 64

The IAPAC Board of Trustees unanimously elected Joep MA Lange and Suniti Solomon in March 2006 to serve two-year terms as At-Large Trustees representing The Netherlands and India, respectively.

“By electing Drs. Lange and Solomon to our Board of Trustees, we are adding to an already rich body of elected leaders their individual experiences in and dedication to improving the quality of care and support delivered to men, women, and children living with HIV/AIDS,” said Allen I. Freehling, Chairman of the IAPAC Board of Trustees.

Lange is a Professor of Medicine at the University of Amsterdam’s Academic Medical Center, where he also heads the Center for Poverty-Related Communicable Diseases. A former President of the International AIDS Society (IAS), he was one of the earliest advocates of increasing access to antiretroviral therapy in resource-poor settings. In 2000, Lange founded and is Chairman of the PharmAccess Foundation, a non-profit foundation dedicated to rapidly expanding access to HIV/AIDS care and treatment in resource-limited regions of the world.

Recognized as the first physician to detect HIV in the Indian population, Solomon is a Professor of Microbiology in the AIDS Research Cell at the Chennai Medical College, and Director of its Center for AIDS Research and Education. She is also Founding Director of YRG CARE, a nongovernmental organization established in 1993 to offer HIV and sexuality education to adolescents and young adults, voluntary counseling and testing, and HIV impatient care. She is a member of the Advisory Board of the International AIDS Vaccine Initiative (IAVI)-India, a permanent member on the Microbicides Committee of the Indian Council of Medical Research (ICMR), and a member of India’s Country Coordinating Mechanism (CCM) for the Global Fund to Fight AIDS, Tuberculosis, and Malaria.
Retention of health care workers in low-resource settings

Fatu Yumkella

The problem of low retention

The number of health workers employed is an indicator of a country's ability to meet the health care needs of its people, especially the poorest and most vulnerable. Resource-constrained countries committed to the Millennium Development Goals are facing up to the reality that shortages and uneven distribution of health workers threaten their capacity to tackle the HIV/AIDS pandemic, as well as the resurgence of tuberculosis and malaria. Worker shortages are linked to three factors: 1) decreasing student enrollment in health training institutions, 2) delays or freezes in the hiring of qualified professionals, and 3) high turnover among those already employed.

Increasingly, health care managers and organizations are focusing attention on the problem of low retention, recognizing that these losses are costly, negatively affect continuity of care, and raise the potential for turnover of remaining employees who suffer stress and burnout from taking on the additional burden of care. Based on an intensive literature review, this article considers challenges and responses related to retention of health care workers, including the causes of turnover, actions to address turnover, and emerging evidence on retention approaches. The article considers retention primarily in the context of sub-Saharan Africa.

Editor's Note: This article was originally published in Technical Brief No. 1 of the Capacity Project. Additional information about and publications of the Capacity Project can be found on their Web site, http://www.capacityproject.org/.

Turnover and vacancy rate

Turnover and vacancy rate are commonly used indicators for understanding recruitment and retention. Turnover records job moves, including transfers. Vacancy rate is the extent to which an organization has unfilled positions, and the cause for this can be linked to internal as well as external factors. In general, worker flow data sets for developing countries are incomplete and inaccurate, and do not allow for precise measurements of turnover or vacancy rates. Still, available data indicate that many sub-Saharan African countries are experiencing high vacancy rates. Increasing vacancy rates over time almost certainly reflect high turnover.

Reported vacancy rates

- **South Africa**: One third of all public health posts unfilled
- **Malawi**: Vacancy rate of 36% for doctors in public health service
- **Ghana**: Vacancy rate for nurses doubled from 28% to 57% between 1998 and 2002

The causes of turnover

For health managers and organizations to feel empowered to reduce uncontrolled turnover, it is important for them to understand the characteristics of workers who are at risk of moving, the patterns of movement—in-country versus out-migration—and the reasons why workers make a decision to leave. The rising trend in out-migration is of concern because these losses reduce a country's labor supply and further weaken health system capacity to tackle priority health problems. Poor financial compensation and unsatisfactory working conditions are emerging as the most likely "push factors" causing workers to move between sectors or cross borders.

**Poor financial compensation**: Health workers are often willing to leave their posts for higher pay elsewhere. A pattern has emerged in which workers are seeking better-paid jobs not only in developed countries but also in less poor countries within their regions. Physicians from Ghana and Zambia who emigrate to the United States can expect to earn up to 20 times more pay, while junior doctors from those countries can earn five times more by moving to Lesotho, Botswana, or South Africa to work. Out-migration for higher pay is assumed to be playing a part in the situation in Zambia, where only 50 of over 600 medical graduates trained between 1997 and 2000 were still working in the country's public-sector services as of 2000. Salary outranked all other factors when health care professionals were asked what would make them remain in their home country. The majority in Cameroon (68%), Ghana (81%), South Africa (78%), and Uganda (84%) implied that an improvement in salary structures would be a good reason to stay.

**Unsatisfactory working conditions**: Many studies have shown, however, that financial compensation alone does not explain migration decisions. For example, South African health professionals are more likely to cross borders than Ugandan professionals, even though pay is lower in Uganda. Turnover is often influenced by dissatisfaction with one or more attributes of the work environment, such as:

- Deteriorating living and working conditions
- Weak performance management, leadership, and supervision structures
• Inadequate equipment and supplies
• Lack of recognition for good work
• Stress due to heavy workload
• Gender-related issues, including sexual harassment and gender-based discrimination
• Limited opportunities for career development and advancement
• Safety and security concerns, including those related to HIV/AIDS protection, care, and risk

“I never thought I would be one of the nurses leaving. I criticized many of my colleagues when they left. Then I found that those of us who were left had to carry the load. In my hospital we had one nurse to 18 beds; there were about 500 outpatients a day and only 14 to 15 nurses allocated to this section. How can we give good care in these conditions? On top of all this, nurses are constantly criticized and picked on.” – South African nurse who left for the US, 2000

“The lack of equipment and lack of drugs is very frustrating and depressing. You cannot do quality work. I have not yet lived up to my own ideal. It is hard under given conditions to achieve one’s goal.”—28-year-old African physician working in the public sector, 2003

Actions to address turnover
Health care managers and organizations have tried a variety of approaches designed to retain valued employees through financial incentives and non-financial incentives, including addressing gender issues and safety concerns.

Financial incentives: While still relatively small in number, there are examples available of the use of financial incentives to address the low-wage situation in resource-constrained countries. The South Africa Department of Health introduced a “rural and scarce skill” allowance in 2003 to attempt to curtail the alarming number of health workers opting to work in other countries. In 2000, Ghana implemented an Additional Duty Hours Allowance scheme intended to help curtail out-migration of doctors. Zambia’s successful proposal to the Global Fund to Fight AIDS, Tuberculosis and Malaria, Round 4, allowed the government to subsidize salaries by about 50% for 972 doctors and clinical officers and 4,292 nurses as a form of motivation for workers so that antiretroviral (ARV) drug scale-up targets will be achieved.

Non-financial incentives: Given the difficulty of providing financial incentives, governments in some resource-constrained countries have explored other avenues to offer in-kind benefits to professional workers. Malawi is among a few sub-Saharan countries to provide housing facilities. Ghana distributed cars but gave priority to doctors who were members of the medical association. A work improvement initiative in Tanzania attempted to link good management practices, worker satisfaction, and retention; two districts received support under the Tanzania Essential Health Project (TEHIP) to install two-way radios at selected facilities to improve communications and reduce time lost to travel. Swaziland and Malawi responded to complaints about career opportunities being biased in favor of doctors by revising career structures to improve progression opportunities for all cadres. The Ghana Medical Association is spearheading proposals for shorter locally based post-graduate medical training to provide career advancement and foster retention. Namibia has developed a comprehensive policy and legislative framework to address workplace discrimination against people living with HIV/AIDS.

Emerging evidence on retention approaches
The literature reviewed for this paper contains a decent number of suggested approaches for improving retention, and examples of approaches under implementation. However, few of these approaches have been evaluated and much of the available evidence about the variables that affect retention is anecdotal. A multi-country study conducted by Gesellschaft für Technische Zusammenarbeit (GTZ) suggests that refresher training opportunities led to high retention in Zambia, while in Ethiopia a mix of continuing education, provision of housing, and establishment of clear career structures is claimed to have resulted in improved job satisfaction and retention. Preliminary findings suggest that as a result of South Africa’s “rural and scarce skill” allowance, more health professionals will likely alter their short-term career plans in favor of staying in post. Researchers have concluded that Ghana’s Additional Duty Hours Allowance has slowed out-migration of doctors and resulted in the shift of doctors from the private to the public sector. In Uganda there is a belief that private not-for-profit organizations are losing providers to the public sector because of increased compensation in the public sector. A convincing case showing a link between financial compensation, motivation, and retention is drawn from a study targeting lower-level health workers in Gongola State, Nigeria, where male community health workers (CHWs) with relatively higher remuneration stayed on average for 3.25 years compared to two years for male CHWs with lower pay.

Conclusions
While the literature contains evidence-based examples of the importance of and causes for turnover, evidence-based information on tested approaches to improve retention remains scarce. Notwithstanding this limitation, anecdotal findings suggest health care managers and organizations should examine three opportunity areas—financial compensation, improving the work environment, and strategies to manage migration—in determining which approach or combination of approaches will deliver the greatest potential impact on maintaining a qualified workforce.

Financial compensation: The literature suggests that retention solutions for resource-constrained countries should address the challenge of low wages if health goals are to be achieved. Skeptics may ask, “What else is new?” or “What about sustainability?” As witnessed in Zambia, what is new is the emerging shift among donors toward providing funding support to cover wages in addition to training and technical activities. In consideration of the sustainability issue, the World Health Organization (WHO) has proposed that a proportion of all donor funding be allocated to the health workforce, with no stipulation about the way the funds are to be spent. Countries would then have a choice as to whether to spend part of the funds for salary supplements.

Improving the work environment: Retention solutions must also seek to enhance the work environment, which is often a significant "push factor" and cause of job dissatisfaction. The literature suggests that health workers are more likely to remain with organizations that offer a combination of benefits to boost job satisfaction. These may include:
• Non-financial incentives (eg, housing, opportunities for training)
• Opportunities for career advancement
• A constructive work environment, including supportive supervision
• Strategies to address gender-related issues and safety concerns related to HIV/AIDS infection

Given resource limitations, many health care managers and organizations will need to choose which areas of the work environment to address first in order to yield quick and sustainable results. In developed countries, more emphasis is increasingly placed on retention approaches that make employees feel valued and supported. For example, employees surveyed from 240 US-based organizations indicate that “trust, concern and support from [the] supervisor” is a key driver of stay or leave decisions. The Sunderland UK national health flexible organizational policy, which provides for special leave, career breaks, and flex-time, is said to have resulted in reduced absenteeism and an increased number of nurses choosing to return to work after having children.

Strategies to manage out-migration: Governments are urged to combine policies for worker retention with policies that will buffer the effect of turnover, especially turnover due to out-migration. Such policies include: 1) alternative staffing strategies to reduce the overdependence on cadres more likely to migrate, 2) compulsory and well-managed community service and bonding schemes tied to an incentive scheme, 3) innovative contracting arrangements, including “secondment arrangements” that will convert to financial gain for valued employees, and 4) creative approaches aimed at improving productivity of present health care workers, which may prove far less expensive than persistently having to recruit, prepare, and deploy new ones.

Developing countries planning to introduce or strengthen worker retention approaches can build the evidence base on retention by:

• Gathering data from existing workers as well as from workers who have moved between sectors or left the health sector, to determine factors that cause workers to make a decision to leave
• Designing retention approaches based on the data gathered
• Tracking which retention approaches work best through sound monitoring and evaluation systems.

Retention approaches and approaches to manage migration—case examples from sub-Saharan Africa

Retention approaches

Financial Incentives

- **Zambia**: Increased salaries for doctors, lab technicians and nurses to enhance ARV scale-up
- **Ethiopia**: Increasing per diem
- **Namibia**: 30% overtime allowance for nurses and generous end-of-service payments
- **Ghana**: Additional Duty Hours Allowance, especially for physicians
- **South Africa**: Rural and scarce skill allowance

Non-Financial Incentives

- **Zambia**: Refresher training
- **Ethiopia**: Mix of continuing education, housing provision, and establishment of clear career structures
- **Tanzania**: Improved facility-related communications and transportation
- **Botswana, Namibia**: Established set of benefits for nurses, including housing, car loans, and medical allowance
- **Ghana**: Car and housing loan schemes for rural-based professionals

Career Advancement Opportunities

- **Ghana**: Proposal for more opportunities for two-year post-graduate training program
- **Ghana, Namibia**: Relaxing eligibility criteria for promotion
- **Swaziland, Malawi**: Improved progression opportunities for all cadres

Workplace Safety/HIV/AIDS Care

- **Namibia**: Capacity building of local NGOs and institutions to provide a comprehensive HIV/AIDS workplace package to private, public, state and local government sectors
- **Tanzania**: Limited home ownership schemes introduced by Kahama Mining Corporation to decrease risky behavior resulting from separation from families

Approaches to manage migration

Alternative Staffing Arrangements

- **Tanzania**: Clinical officers, deployed at all levels, trained to perform voluntary surgical contraception, which was previously done exclusively by doctors
- **Kenya**: Clinical officers deployed at all levels, including dispensaries
- **South Africa**: Task team commissioned to develop guidelines for Doctor Assistant program
- **South Africa**: Suggestion to increase proportion of black medical students, who are less likely to emigrate

Community Service and/or Bonding Schemes

- **Ghana**: Proposal to reintroduce three to five year bonding schemes for doctors
- **South Africa**: One year of compulsory community service for doctors and dentists on completion of training

Creative Contracting Arrangements

- **South Africa**: Through agreement between South Africa and the United Kingdom, South African professionals work in the United Kingdom National Health Service and UK staff serve in rural parts of South Africa
- **Zambia**: Explored de-linking health commission from civil service so that staff could be hired on renewable contract allowing for higher salaries
- **Ghana**: Allows public-sector pharmacists to work for private for-profit sector

Fatu Yumkella is a Performance Support Specialist at IntraHealth International in Chapel Hill, North Carolina.
Adherence matters
Continued from page 60

the disease, acquiring resistance to the still limited number of antiretroviral drugs currently available.

While we have learned much about the measurements, correlates, and outcomes of adherence to antiretroviral therapy since its advent in 1996, our knowledge is based upon previously en vogue, partial suppressive antiretroviral regimens administered to limited numbers of patients. A recent conversation with a subject matter expert during the 2006 NIMH/IAPAC International Conference on HIV Treatment Adherence — held March 8-10, 2006, in Jersey City, New Jersey — revealed the following unanswered questions:

- How do the complexities of adherence behavior that are not captured by a simple percentage of missed doses influence virologic and clinical outcomes?
- Has the association between adherence and treatment outcomes changed with the advent of newer, longer half-life antiretroviral drugs?
- Does adherence behavior determine whether patients develop either limited or multi-drug resistance mutations?
- How much adherence is necessary to prevent disease progression and death?

In theory, perfect adherence to antiretroviral therapy will prevent any viral evolution, and guarantee that antiretroviral drugs work without losing their potency. The goal of antiretroviral therapy thus remains perfect adherence and complete viral suppression. Yet, troubling evidence periodically emerges that even successful antiretroviral regimens adhered to faithfully fail, and an on-line survey described in the January 2006 issue of the IAPAC Monthly revealed that a significant number of patients do not understand what it takes to achieve full adherence.6

These are important questions with equally important implications for the future of antiretroviral therapy. If we do not address them now, we risk another generation of death and destruction wreaked by HIV disease, though this time it will have been preventable. Whatever the response to the numerous questions left unanswered, to quote David Bangsberg and Steven Deeks (both of the University of California, San Francisco): “If patients are treated, they will do better. And if they improve their adherence to near-perfect levels, they will do even better.”7

José M. Zuniga is President/CEO of the International Association of Physicians in AIDS Care (IAPAC), and Editor-in-Chief of the IAPAC Monthly.

Reference
5. The HERO (HIV Epidemiology Research on Outcomes) Adherence Study was conducted by the Albert Einstein College of Medicine from 1998 to 2004 and involved a 113-patient cohort followed for six months.
6. CCTG (California Cooperative Treatment Group) 578 was conducted by the RAND Corporation from 2000 to 2002 and involved a 199-patient cohort followed for 48 weeks.
A

tazanavir (ATV) boosted with low-dose ritonavir (RTV) is as effective as lopinavir/ritonavir (LPV/r) at suppressing viral load over two years in treatment-experienced patients when combined with tenofovir (TDF) and a nucleoside reverse transcriptase inhibitor (NRTI), according to results from a study conducted by atazanavir’s manufacturer, Bristol-Myers Squibb, and published in the March 21, 2006, edition of the journal AIDS.

A favorable safety profile for ATV also emerged in the study. The investigators found that patients taking ATV were less likely to experience diarrhea than individuals taking LPV/r, and that ATV-treated patients had an improvement in their lipid profile from baseline whereas individuals on LPV/r experienced an increase in their blood fats and sugars.

BMS Study 045

A previously published analysis of the first 48 weeks of BMS Study 045 showed that, in patients who had experienced virologic failure on two earlier potent antiretroviral regimens, a regimen based on ATV/r was likely to achieve as large and durable a reduction in viral load as an antiretroviral regimen based upon LPV/r. Patients in both arms of the study also took TDF and an NRTI, which, whenever possible, was selected by resistance testing. The trial was randomized, open-label, and involved 347 individuals.

The investigators extended their analysis to 96 weeks. Once again, they wished to see if ATV/r achieved and maintained viral suppression comparable to LPV/r. They also had a number of secondary objectives. These included the number of patients in each arm of the study with a viral load below 400 copies/mL and 50 copies/mL, respectively, after two years of treatment, and the increase in CD4 count from baseline.

They also wished to compare the safety and side effect profile of the two study drugs.

96-week results

Over two years, ATV/r had comparable virologic efficacy to LPV/r. The mean
reduction in viral load from baseline was -2.29 log_{10} copies/mL among patients taking ATV/r and -2.08 log_{10} copies/mL among individuals randomized to take LPV/r. Similar proportions of patients in both arms of the study achieved a viral load below 400 copies/mL and 50 copies/mL, respectively.

Further analysis was conducted to see if the number of baseline protease inhibitor (PI) resistance mutations influenced the effectiveness of the two study drugs. The investigators found that among patients with fewer than four resistance mutations, the median fall in viral load was -2.47 log_{10} copies/mL in the ATV/r arm and -2.21 log_{10} copies/mL in the LPV/r arm. If a patient had four or more PI resistance mutations, the median reduction in viral load was -1.71 log_{10} copies/mL if they were taking ATV/r and -1.81 log_{10} copies/mL if they were taking LPV/r.

After 96 weeks of treatment, CD4 counts had increased from baseline by 160 cells/mm³ in the ATV/r arm and by 142 cells/mm³ in the LPV/r arm. All differences were non-significant.

Safety and side effects

The investigators then looked at the safety profile of the two study drugs. Over the 96 weeks of the study, a severe adverse event was experienced by 13% of patients taking ATV/r and 11% of patients taking LPV/r. Two individuals taking LPV/r died as did one person taking ATV/r, but none of these deaths were related to the study drugs.

Significantly more patients taking LPV/r (19%) experienced mild to severe gastrointestinal problems than those taking ATV/r (9%, P < 0.05). In addition, diarrhea was more common among LPV/r-treated patients (13% versus 3%, P < 0.01).

Attention was then turned to the effect of the two study drugs on patients’ lipid profiles. Two years of treatment with LPV/r resulted in a mean 9% increase in total cholesterol and a 30% increase in fasting triglycerides, whereas ATV/r-treated patients experienced a mean fall from baseline in total cholesterol of 3% and a 13% fall in fasting triglycerides (P < 0.0001).

As expected, jaundice and increases in bilirubin were associated with ATV treatment. A total of 53% of those taking ATV experienced a moderate to severe increase in their bilirubin compared to less than 1% of patients taking LPV/r. However, although there were a total of 29 cases of hyperbilirubinemia among patients taking ATV, only five occurred during the second year of therapy with the drug, and nobody stopped treatment because of this side effect.

The higher incidence of diarrhea and lipid increases among the LPV/r-treated patients meant that these individuals were much more likely to require anti-diarrhea treatment (25%) than those taking ATV/r (6%, P < 0.0001). Patients taking LPV/r were also significantly more likely to require lipid-lowering therapy than individuals taking ATV/r (20% versus 9%, P < 0.05).

The investigators conclude that ATV/r showed comparable “durable efficacy to [LPV/r] and was not associated with unexpected or late-emerging adverse events” when used in combination with TDF and an NRTI in treatment-experienced patients. They add “the long-term use of [ATV/r] may decrease pill burden, improve tolerability, and provide sustained virologic suppression for antiretroviral-experienced patients with HIV infection.”

Reference

The International Association of Physicians in AIDS Care (IAPAC) presents:

IAPAC North American Sessions 2006

May 11-12, 2006

University of Chicago
Gleacher Center

Program:
- Implications of a Decade of HAART
- Navigating ARV Drug Resistance
- Sociobehavioral Aspects of HIV Care
- Emerging Issues in HIV Care

Continuing Education:
This activity is jointly sponsored by the University of Medicine and Dentistry of New Jersey and IAPAC. This activity has been approved for AMA PRA Category 1 Credits™.

Co-Chairs:
Carol Harris, MD, MSc, Albert Einstein College of Medicine
Renslow Sherer, MD, University of Chicago

Accommodations and Travel:
Attendees are responsible for their own travel and hotel arrangements. Visit www.iapac.org for a list of nearby hotels.

Registration:

<table>
<thead>
<tr>
<th></th>
<th>IAPAC Members</th>
<th>Non-Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (Until February 28, 2006)</td>
<td>US$100</td>
<td>US$200</td>
</tr>
<tr>
<td>Regular (March 1-April 30, 2006)</td>
<td>US$150</td>
<td>US$250</td>
</tr>
<tr>
<td>Late (May 1-10, 2006)</td>
<td>US$200</td>
<td>US$300</td>
</tr>
</tbody>
</table>

Questions?
Contact Aimee Clark at (312) 795-4934 or aclark@iapac.org.
13th CROI surprise:
Antiretrovirals are good for you
With a flourish of studies on structured treatment interruptions (STIs) and the cardiovascular complications of HIV infection and its therapies, the 13th Conference on Retroviruses and Opportunistic Infections (CROI) may prove a turning point in the management of this pernicious disease.

And the point returned to may be one set 10 years ago, suggested antiretroviral maven John Mellors (University of Pittsburgh). While other CROIsters harked back to the discovery of AIDS a quarter century ago or the 10th birthday of triple therapy, Mellors pointed to a single study—AIDS Clinical Trials Group (ACTG) protocol 320, the randomized trial that ratified the life-saving advantage of three antiretrovirals over two.

Speaking after six STI researchers served up fresh results—some of them mixed, some plainly awful—Mellors suggested “it’s ironic and fitting that we’ve learned what we already knew.” ACTG 320 showed that triple therapy “was life-saving and most important for people with an AIDS diagnosis and a low CD4 count,” he observed. “Ten years later we’ve found that people with an AIDS diagnosis and a low CD4 count still need that therapy.”

That discomfiting assessment may oversimplify what these latest STI trials mean, argued Staccato study chief Bernard Hirschel (University Hospital of Geneva). A person just starting antiretrovirals with a red-alert CD4 count, as in ACTG 320, is not the same as someone whose CD4 count drops toward the danger zone when that person suspends a regimen that worked for years.

But there was no escaping the humbling “rediscovery” that taking potent antiretrovirals day after day is good for people with HIV infection—better, two trials showed, than taking antiretrovirals part time. Both the massive multinational SMART study [abstract 106LB] and the smaller Trivacan trial in Côte d’Ivoire [abstract 105LB] logged more than twice as many cases of HIV disease progression or death among people who timed drug breaks to CD4-cell swings rather than taking steady therapy.

Even more astonishing to some drug-holiday apologists, both randomized trials unhasped a pivotal linchpin of STI thinking—that on-and-off therapy trims the risk of complications typically blamed on antiretrovirals, namely heart, liver, and kidney disease. Far from improving quality of life, in both SMART and Trivacan drug breaks put more people in the hospital—or the morgue—some with distinctly non-AIDS diagnoses. And it happened so fast that independent review panels had to shut SMART down early and close the CD4-guided arm in Trivacan.

Staccato, the third large randomized comparison of CD4-steered breaks versus unremitting therapy detailed at CROI, did not find a higher progression risk in the off-and-on arm [abstract 102]. Different CD4 stop and start signals in Staccato, and other variables considered below, may explain this happier outcome.

But when CROI roundtable chair Scott Hammer (Columbia University, New York) asked five STI experts if “CD4-guided STIs should be reserved for clinical research” until statisticians finish digesting these latest results, everyone agreed. And Staccato’s Bernard Hirschel was one of those experts. Indeed, in a post-CROI e-mail to the IAPAC Monthly, he professed seeing

Though the wisdom of nature can reason it thus and thus, yet nature finds itself scourged by the sequent effect.

—William Shakespeare, King Lear (I, ii, 113-115)
no immediate need for further STI trials, at least until SMART’s stat chefs hash through all the data.

Besides what these STI trials say about suspending antiretrovirals, the next most burning question is what they say about cardiovascular disease in people with HIV. This year’s CROI also featured another iteration of the vast Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, confirming a higher risk of heart attacks with each extra year of therapy and now squarely placing the blame on protease inhibitors (PIs) [abstract 144]. But the relative rate (RR) of myocardial infarction (MI) has been dropping in this 11-cohort study, perhaps because people are switching from PI, or starting antilipid therapy, or stopping smoking (see “MI rates drop in D:A:D,” page 80).

Another variable almost certainly contributes to these seesaws MI rates: HIV itself. Uncontrolled or poorly controlled HIV infection sparks inflammation—particularly in endothelial cells that line blood vessels. At the same time the virus apparently promotes thicker and tougher artery walls. And HIV probably contributes to pulmonary hypertension, as more CROI studies confirmed. All these things make the heart’s job harder.

Do the HIV rebounds and immune upsets that invariably follow drug breaks threaten blood vessels enough to explain the higher heart disease risk in SMART’s drug holiday arm? No one can say. But mounting evidence from that seminal trial, from other STI studies, and from research results stretching back several years, offer at least a loud hint that letting HIV off the antiretroviral hook poses clinical risks beyond progression to AIDS.

ARE THERE ANY SMART STIs?

If no one has found an STI that confers some advantage to people with HIV, no one can blame lack of high-flying hypotheses, each run to ground by dogged research. The appealing theory that dosing the immune system with STI-fed boosters of HIV itself fell short in people with chronic infection.\(^2^4\) then in people with primary infection.\(^5^7\) And evidence-based speculation that drug breaks would render HIV wobbly-kneed when facing well-planned salvage regimens fell flat.\(^6^8\)\(^-^1^1\)

Yet more than one cohort study hinted that drug breaks seemed safe in people whose CD4s climbed high with an antiretroviral boost or in those who started therapy with a T-cell count no longer considered a treatment start signal. Indeed, 48-week results of the randomized Staccato trial comparing steady therapy, drug holidays guided by CD4 ups and downs, and week-on-week-off (WOWO) therapy in 74 people showed comparable clinical outcomes in the continuous-therapy arm and CD4-guided group.\(^1^2\) WOWO proved a no-no, with a 31% virologic failure rate.

Curiously, people told to shelf their HIV meds in Staccato and other small studies rarely enjoyed the bennisons of freshly regulated lipids, newly controlled glucose, or falling liver enzymes,\(^1^2^\)\(^-^1^5\) though people taking their drugs staccato in Staccato did have self-reported lipodystrophy significantly less often than people in the control arm after 24, 48, and 72 weeks.

Then came SMART, surely the weightiest STI study ever. Its sheer size, its simple design, and its vow to pile up plentiful endpoints over eight years impressed many. But one morning a month before CROI, STI adherents and skeptics alike opened their e-mail and felt still-uncaffeinated eyes glaze further upon reading this headline: “International HIV/AIDS trial finds continuous [therapy] superior to episodic therapy.”\(^1^6\)

SMART was over. After only an average 14 months of follow-up, instead of the anticipated 96, SMART’s data and safety monitoring board (DSMB) had seen enough.

At least the randomized trial is over. The data delving will surely continue for years. But already SMART’s stat team has burrowed through mountains of data and handed the richest diggings to Wafaa El-Sadr (Harlem Hospital, New York), who came to CROI with 18 slides, none bearing good news on CD4-guided STIs [abstract 106LB]. (Slides from this and every talk at the 13th CROI appear on the conference Web site, http://www.retroconference.org/2006.) SMART’s straightforward plan called for signing up 6,000 people with a CD4 count above 350 cells/mm\(^3\), assigning half to continuous therapy and half to drug breaks beginning any time the CD4 count topped 350 cells/mm\(^3\) and ending when the count hit 250 cells/mm\(^3\). Trial designers anticipated 910 primary endpoints—progression to AIDS or death—over an average eight years of follow-up. But in January 2006, with 164 endpoints on the books, and an amazingly low 2% lost to follow-up, it became clear that drug breaks as defined in this trial are fraught with danger.

The DSMB pulled the plug after counting 117 primary endpoints in the CD4-guided arm versus 47 in the steady-therapy group. Trial planners projected an overall progression or death rate of 1.3% per year in the first 24 months, and that’s about the rate they saw in the continuous-therapy arm—1.5 per 100 person-years. But the treatment-break arm chalked up an event rate of 3.7 per 100 person-years. Statisticians figured a 2.5 times higher risk of progression or death in the CD4-guided arm (95% confidence interval [CI] 1.8 to 3.6), a highly significant difference (\(P < 0.0001\)).

People taking drug breaks had a 1.9 times higher risk of death alone, a 6.1 times higher risk of serious progression, a 3.3 times higher risk of nonserious progression, and a 2.2 times higher risk of serious progression or death.

Bad enough, but then El-Sadr delivered what may be the coup de grâce for this kind of STI: compared with the continuous-therapy arm, the STI group suffered more “severe complications,” which meant cardiovascular-, hepatic-, or renal-related deaths, or nonfatal heart, liver, or kidney complications. A composite endpoint conflating all these endpoints—the very setbacks drug holidays look to avert—proved 50% more likely in the holiday group.

SMART also shredded another shibboleth of STI hermeneutic—that people with higher pretreatment CD4 nadirs can take longer drug breaks safely. Splitting CD4 nadirs into six echelons, SMART’s number nudgers saw almost no difference in progression rates. For example, people with a CD4 nadir under 50 cells/mm\(^3\) had
a 2.9 times higher risk of progression or death than the control arm, precisely the same risk as people with a nadir between 200 and 299 cells/mm³.

Nor did CD4 count at the beginning of SMART affect progression rates. Indeed, the risk of progression proved lower (but still bad) in the lowest CD4 bracket, 350 to 459 cells/mm³ (odds ratio [OR] 1.5), than in the higher CD4 brackets (OR 4.3 for 450 to 549 cells/mm³, OR 3.1 for 550 to 649 cells/mm³, and OR 2.9 for 650 or more cells/mm³). The CD4 count measured on the study visit just before an endpoint “event” did not predict those endpoints. Finally, having AIDS at study entry—as 24% of these people did—had no effect on progression risk.

Strictly speaking, all these results pertain only to the population studied, fewer than 5% of whom began SMART with no antiretroviral experience, 24% of whom already had an AIDS diagnosis, and 30% of whom enrolled with a viral load above 400 copies/mL. Yet a study of the same CD4-guided tactic in younger West African adults, all with viral loads under 300 copies/mL, yielded almost precisely the same risk of progression (see “Trivacan,” below).

Whereas 74% of SMART enrollees were men, 77% in the African Trivacan study were women. Trivacan participants had a median age of 34 years, compared with 46 years in SMART. But statistical analysis showed that neither age nor gender swayed progression risk in SMART.

Any way you look at it, SMART upends several tenets of STI thinking. Writing for the Web site of the National AIDS Treatment Advocacy Project (NATAP), David Margolis (University of North Carolina, Chapel Hill) calls the higher non-AIDS complication rate in the drug-break arm a “particularly powerful” finding because “it is directly in opposition to the hypotheses that the SMART study investigators sought to prove.”17

And that’s not the only theoretical turn-around SMART turned up. In CROI notes shared with the IAPAC Monthly (and reviewed by SMART’s top statistician), STI expert Bernard Hirschel spells out several more (Table 1).

Trivacan: a CD4 STI flop in Africa

Few expressed surprise that potent antiretrovirals work in Africa, just as they do on other continents.

### Table 1. Expectation and reality in SMART: Notes from Bernard Hirschel and James Neaton

<table>
<thead>
<tr>
<th>Item</th>
<th>Expectation</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining opportunistic infections/death</td>
<td>Steady-therapy arm will do modestly better in the short term but worse in the long run. SMART powered to detect a 17% relative reduction in hazard in the STI arm versus steady therapy. Expected event rate in the steady-therapy arm will be about 1.3% per year for the first 2 years, then 2.6% per year.</td>
<td>Steady-therapy arm yields many fewer endpoint events than STI arm. Event rate in steady-therapy arm is similar to that projected—1.5 per 100 patient-years, compared with 3.7 per 100 patient-years in the STI arm, for a relative risk of 2.5, P &lt; 0.0001.</td>
</tr>
<tr>
<td>Major toxicity</td>
<td>The STI arm will have less drug exposure and therefore less toxicity.</td>
<td>STI arm has higher “toxicity,” with a relative risk of 1.6 for serious side effects, P = 0.04.</td>
</tr>
<tr>
<td>Relation to CD4 count</td>
<td>If there is a difference in AIDS-related events, it will be linked to lower CD4 counts in the STI arm. In patients with high CD4 counts, the difference between arms will disappear.</td>
<td>Lower CD4 counts may not explain all the difference between the two arms. Even at high CD4 counts, STI arm is worse than steady-therapy arm.</td>
</tr>
<tr>
<td>Deaths</td>
<td>Increased mortality in the STI arm will be linked to AIDS.</td>
<td>Mortality in STI arm is higher than in the steady-therapy arm, but only 3 of 44 deaths are “AIDS-related.”</td>
</tr>
<tr>
<td>Rate of events in STI arm</td>
<td>Event rate will be lower than or equal to that of historical cohorts with similar CD4 counts before treatment was available.</td>
<td>Preliminary analyses suggest the event rate may be higher in SMART’S STI arm.</td>
</tr>
<tr>
<td>Influence of CD4 nadir</td>
<td>Event rate will be worse, and risk ratio (STI/steady therapy) higher in those with lower nadir.</td>
<td>Nadir doesn’t make any difference.</td>
</tr>
</tbody>
</table>

Source: Bernard Hirschel, University Hospital of Geneva, James Neaton, University of Minnesota, Minneapolis. (Hirschel, who ran the SMART trial in Switzerland, drafted this table. Neaton, chief statistician for SMART, reviewed and revised the table.)

As in earlier reports on Staccato, setting off on drug holidays didn’t do much to rein in jumpy lipids. The steady and STI arms did not differ in triglyceride changes.
So should anyone be shocked that CD4-guided antiretroviral breaks fail in Africa, just as they do elsewhere?

At least when governed by a 350-cells/mm³ stop sign and a 250-cells/mm³ green light in Côte d’Ivoire—the same stop and go signs SMART used—drug breaks proved as dangerous in Africa as elsewhere [abstract 105LB]. The incidence rate ratio for serious morbidity measured 2.6 (95% CI 1.3 to 5.6) in the CD4-guided arm compared with continuous therapy, nearly mirroring SMART’s 2.5 OR for progression with CD4-regulated breaks.

Christine Danel (University of Treichville, Abidjan) reported 17.6 cases of serious morbidity per 100 patient-years in the STI arm versus 6.7 in the steady-therapy group. People stopping and restarting antiretrovirals had a 1.5 times higher incidence of tuberculosis, a 2.6 times higher incidence of oropharyngeal candidiasis, and a 15.9 times higher incidence of invasive bacterial infection than people who never took a drug break.

Most of the bacterial infections—which drove the higher STI-group morbidity rate—happened at CD4 counts above 250 cells/mm³. And everyone continued cotrimoxazole prophylaxis during the study; 85% of those with bacterial infections had cotrimoxazole-resistant bacteria.

After an average 19.4 months of follow-up, Danel counted 0.6 deaths per 100 patient-years in the ongoing-therapy group and 1.2 deaths per 100 patient-years in the CD4-guided group. With these results in hand, the Trivacan safety panel shut down the CD4 STI arm but allowed researchers to continue comparing steady therapy with a two-month-off-four-month-on strategy.

Trivacan enrolled 651 adults with a median age of 34 years, a CD4 count above 350 cells/mm³, and a viral load below 300 copies/mL and assigned them in a 3-2-1 ratio to two-month-off-four-month-on STIs, CD4-guided breaks, or continuous therapy. Median nadir CD4s measured 272 cells/mm³ in the 216 people assigned to CD4-guided STIs and 274 cells/mm³ in the 110 who never stopped therapy. Respective median baseline counts stood at 457 and 461 cells/mm³.

Higher morbidity rates in the CD4-managed group meant those people spent significantly more time in the hospital than people who continued treatment (68 versus 36 days, \( P < 0.001 \)) and had more clinic visits (233 versus 159, \( P < 0.001 \)). Researchers often proffer cost savings as one rationale for STIs in poor countries, but in this trial extra care for the STI group probably ate up any money saved on drugs. (Danel did not have a cost analysis.) Genotyping spotted twice as many resistant samples in the drug-break group (11% versus 5%), though the difference fell short of statistical significance in this small study group (\( P = 0.13 \)).

Did drug breaks have a big impact on toxicity? No. After 12 months of study, rates of low-density lipoprotein (LDL) cholesterol, high glucose, self-reported lipodystrophy, and arterial hypertension were only marginally lower in the drug-break group. The break takers had modestly higher rates of anemia (low red cells) and thrombocytopenia (low platelets) than the always-on group, and similar rates of neutropenia (low white cells) and elevated liver enzymes.

A minority vote from Staccato

Alone among CROI trials with CD4-guided arms, Staccato found that strategy as safe as continuous therapy [abstract 102]. Although week-on-week-off therapy bred virologic failure in this 430-person study, Jintanat Ananworanich (HIVNA T, Bangkok) reported no viral control difference between the steady-therapy group (91.8% below 50 copies/mL) and the CD4-guided group (90.3% after treatment resumed). No one in either group added an AIDS diagnosis to their chart, and one person in each group died.

If Staccato’s holiday takers had the same progression rate as break takers in SMART, Staccato chief Hirschel observes in notes shared with the IAPAC Monthly, they would have endured 15 to 20 such “events.” But they suffered only one—a death from colon cancer.

Compared with unceasing therapy, CD4-timed breaks yielded higher rates of oral and vaginal candidiasis (\( P = 0.03 \)) and thrombocytopenia (\( P = 0.06 \)). People who never interrupted therapy had more neuropathy (\( P = 0.03 \)) and diarrhea (\( P = 0.04 \)). Of course CD4 counts dipped during the drug breaks (see “Trying to explain the differences,” below). These ups and downs led Margolis to observe that “one seems to be trading one set of adverse events for another, at the cost of lower CD4 counts.”

As in earlier reports on Staccato, setting off on drug holidays didn’t do much to rein in jumpy lipids. The steady and STI arms did not differ in triglyceride changes. Although the STI group ended up with a lower median cholesterol reading (4.6 versus 5.0 mmol/L, or 161 versus 193 mg/dL), both group levels lie in the optimal range. Resistance mutations emerged no more often with drug breaks than with steady therapy.

Trying to explain the differences

Why did CD4-steered STIs work in Staccato enrollees (about 80% of them Thai) and not in Trivacan or SMART? CD4 stop and start thresholds were the most obvious difference. Whereas Trivacan and SMART break takers resumed treatment only at a CD4 count of 250 cells/mm³, Staccato participants ended drug holidays as soon as the count slipped under 350 cells/mm³.

But Hirschel doesn’t think CD4 thresholds hold the whole answer. Other differences he and Jintanat noted (Table 2) were the longer median pretreatment treatment durations in SMART (72 months versus 15 months in Staccato) and the older median age in SMART (46 years versus 34 years in Staccato). But how these differences explain the divergent results remains unclear, Hirschel adds. Indeed, younger age didn’t help Trivacan’s African break takers. And Trivacan enrollees had even less prestudy antiretroviral experience than Staccato participants.

So one comes back to the CD4 cutoffs. How many rich-country clinicians these days would let a treatment-naive person drift under 250 cells/mm³—the SMART and Trivacan restart flags—without getting edgy? Does it make more sense to let CD4s drop that low in people with a seven- or 72-month treatment history who may have a CD4 nadir under 200 cells/mm³, an AIDS diagnosis, or resistance mutations?
But baseline AIDS, baseline CD4s, and CD4 nadir had no apparent tie to progression risk in SMART. And only a handful of SMART break takers ever registered a count below 200 cells/mm$^3$ during treatment suspensions (Table 3). SMART’s STI assignees spent considerably more patient-years below 250 cells/mm$^3$, and more still below 350 cells/mm$^3$, especially when compared with the no-break group. More than one third of break takers in Staccato saw their T-cell counts waltz under 350 cells/mm$^3$, compared with 4% in Staccato’s always-on group. And SMART break takers spent almost one third of their patient-years under 350 cells/mm$^3$, compared with 8% of patient-years in SMART’s steady arm.

These rates suggest at least two interpretations:

1. Something bad happens when CD4 counts drop under 350 cells/mm$^3$. SMART was big enough to tell the difference; Staccato wasn’t. In his analysis of Staccato, Margolis argues “it is not clear that the [Staccato] study was long enough or large enough to detect differences in event rates between this [under-350] subset of the [STI] group and the continuous therapy group.”

2. It doesn’t matter much if a CD4 count falls a little under 350 cells/mm$^3$, as it did so often in the STI arms of both Staccato and SMART. But in a big trial like SMART, even a few drops below 250 or 200 cells/mm$^3$ are enough to rock the clinical Richter scale.

Another study detailed at CROI sheds light on this question. Charting opportunistic infection (OI) incidence in people with CD4 quotients assumed to protect against certain OIs, EuroSIDA researchers confirmed low rates of such rude surprises in 11,229 cohort members [abstract 783]. But the six OIs studied proved much more likely at these presumed “high” CD4 counts among people not taking a potent regimen.

Amanda Mocroft (Royal Free Hospital, London) and the EuroSIDA team looked for cytomegalovirus (CMV), Mycobacterium avium complex (MAC), or toxoplasmosis in people with more than 100 cells/mm$^3$, Pneumocystis pneumonia or esophageal candidiasis in people with more than 200 cells/mm$^3$, and tuberculosis (TB) in people with more than 300 cells/mm$^3$. They tallied only 212 such OIs, but incidence per 1,000 patient-years proved consistently higher in people not taking a stout regimen:

- 4.0 versus 1.0 per 1,000 patient-years for CMV, MAC, and toxoplasmosis
- 8.0 versus 2.5 per 1,000 patient-years for Pneumocystis and candidiasis
- 3.0 versus 0.9 per 1,000 patient-years for TB

Mocroft reckoned that starting potent therapy lowered the risk of the first five OIs by 54%. An even more telling observation, vis-à-vis STIs, was that lower CD4 counts—even those still above 200 or 300 cells/mm$^3$—meant a bigger OI risk. Opportunistic infection incidence per 1,000 patient-years measured 0.1 with a count at or above 500 cells/mm$^3$, 0.4 at 400 to 499 cells/mm$^3$, 1 at 300 to 399 cells/mm$^3$, 2 at 200 to 299 cells/mm$^3$, and 8 at 100 to 199 cells/mm$^3$.

Viral load also made a difference. People with loads topping 1,000 copies/mL ran a 4.4 times higher risk of CMV, MAC, or toxo and a 2.63 times higher risk of Pneumocystis pneumonia or candidiasis (the most common OI in SMART). Perhaps progression risk during STIs reflects not only falling CD4 counts during the drug

---

### Table 2. Differences between CD4-guided STI trials

<table>
<thead>
<tr>
<th></th>
<th>Staccato</th>
<th>Trivacan</th>
<th>SMART</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>430</td>
<td>326</td>
<td>5,472</td>
</tr>
<tr>
<td>p-y follow-up in STI arm</td>
<td>490</td>
<td>—</td>
<td>3,062</td>
</tr>
<tr>
<td>CD4 at stop</td>
<td>350</td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>CD4 at start</td>
<td>350</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>34</td>
<td>34</td>
<td>46</td>
</tr>
<tr>
<td>AIDS or death per 100 p-y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STI</td>
<td>0.2</td>
<td>17.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Steady therapy</td>
<td>0.4</td>
<td>6.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Oral and vaginal candidiasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STI</td>
<td>2.28</td>
<td>6.4</td>
<td>—</td>
</tr>
<tr>
<td>Steady therapy</td>
<td>0.34</td>
<td>2.3</td>
<td>—</td>
</tr>
<tr>
<td>Time on antiretrovirals before study (m)</td>
<td>15</td>
<td>7</td>
<td>72</td>
</tr>
</tbody>
</table>

p-y = patient-years, m = months, y = years.
Source: Ananworanich J et al, abstract 102.
break, but also rebounding viral loads. Finally, just as in SMART, neither nadir nor baseline CD4 count affected OI risk in this EuroSIDA analysis.

The EuroSIDA study did not address non-AIDS progression—the heart, liver, and kidney complications that bedeviled treatment interrupters in SMART. But several other CROI studies—and a rich literature of earlier reports—do suggest some answers about that SMART shocker. This article will consider such studies below (see “HAART, Kidneys, Liver, Heart,” page 79), after reviewing CROI’s other STI trials.

One thing SMART does not say, El-Sadr insisted, is that the relatively low 3% progression rate in the CD4-guided group means this kind of STI is worth the risk. Progression risk rose consistently in the STI group as follow-up continued and would have been worse without a sharpened safety panel. And people inclined to take a drug break can’t hire SMART’s safety watchdogs to monitor their course.

What can one say about Trivacan? Although antiretrovirals came late to Africa—too late for millions—people now beginning therapy have one vast advantage over counterparts in Europe, the Americas, and even Thailand: They can learn from mistakes made in richer countries. Sadly, market forces stuck many Africans (and Thais) with a fixed-dose combination that includes stavudine (d4T), a toxic drug no longer recommended in lands of plenty. One hopes they learn faster about STI failings.

A window half-open or half-shut?
Testing an eight-week-on-eight-week-off strategy in the Window trial (Agence Nationale de Recherches sur le SIDA [ANRS] 106), French investigators decreed this tactic “noninferior” to continuous therapy when the primary endpoint is a confirmed CD4 count under 300 cells/mm³ through 96 weeks [abstract 104]. No one in either study arm added an AIDS-defining diagnosis to their chart or died of AIDS, but the STI group had considerably more minor setbacks than the control arm, and significantly more on/off enrollees lost viral control during the trial.

Bruno Marchou (Purpan Hospital, Toulouse) and ANRS confrères signed up 403 people with a CD4 count at or above 450 cells/mm³ and a viral load below 200 copies/mL for at least six months while taking the same regimen. The protocol excluded people with a CD4 nadir below 100 cells/mm³, anyone taking nevirapine (NVP) or abacavir (ABC), and anyone coinfected with hepatitis B virus (HBV) and taking tenofovir (TDF) or lamivudine (3TC). So Window’s results don’t apply to anyone with those traits.

The study group was a stable contingent of steady responders. Median baseline CD4 count measured 739 cells/mm³ in the STI group and 748 cells/mm³ in the control arm after an average five years of therapy. Only about 20% of enrollees were taking their first regimen when Window opened.

An intent-to-treat analysis at week 96 determined that seven people (3.6%) in the on/off group versus three (1.5%) in the steady-therapy group met the primary endpoint of a confirmed CD4 count under 300 cells/mm³. Despite this more than doubled rate of immunologic failure in the STI arm, the difference met the predetermined criterion establishing intermittent therapy as noninferior to continuous treatment. An on-treatment analysis counted six immunologic failures in the STI arm and only one in the control arm. Even this difference fell within statistical bounds of noninferiority for treatment interruptions.

The ANRS fixed the noninferiority threshold at less than or equal to a 7% difference in the upper bound of the 95% confidence interval when figuring the primary endpoint. The upper bound difference came to 5.6% in the intent-to-treat analysis. Analyzing these results on the NATAP Web site, Margolis suggests that although the number of CD4 drops below 300 cells/mm³ remained small, “an extra handful of events in the [treatment interruption] arm would have made it inferior.” In the on-treatment analysis, the difference in this metric, 6.5%, edged right up to the preset threshold.

In notes shared with the IAPAC Monthly, Hirschel also voices some hesitation about embracing this kind of STI. Although the trial arms did not differ significantly in the proportion with a count below 300 cells/mm³ after 96 weeks of follow-up, he observes, they did differ in the proportion under 400 cells/mm³. And since CD4s drift inexorably downward during drug breaks, “there is a risk of low CD4 counts, were this regimen continued past 96 weeks.”

Although no one in either arm ended up with AIDS before the trial ended, the STI group endured more cases of mucosal candidiasis (10 versus six), thrombocytopenia with bleeding (two versus none), and herpes simplex (four versus two), but not herpes zoster (two versus three). Eleven break takers had grade 3 or 4 thrombocytopenia during the study, compared with two in the steady-therapy group. Three people endured the acute retroviral syndrome when they suspended therapy.

At week 96, after being back on treatment for eight weeks, 81% in the drug-holiday group had a viral load under 400 copies/mL versus 90% in the always-on group, a significant difference (P < 0.02). Seventeen break takers and 14 continuously treated people registered a viral load above 1,000 copies/mL during the trial, a nonsignificant difference.

Margolis makes another piquant point about these high breakthrough rates in a group doing well on therapy for so long. “One wonders if the study selected patients hoping for the [STI] arm,” he muses, “driving up failure rates in the disappointed ones assigned to the [continuous therapy] arm.” If that hunch were true, it would mean STI trials hold dangers for people in steady-therapy arms as well.

One should also note that fixed-interval drug breaks sometimes fail outright, as week-on-week-off interruptions did in Staccato.12

Fixed-interval STIs and resistance
Like the Window trial, the Italian ISS PART study compared fixed-interval treatment interruptions with steady therapy, but the Italians devised a more complex off-and-on sequence [abstract 103]. Lucia Palmisano (Istituto Superiore di Sanità, Rome) and colleagues randomized 273 people taking their first antiretrovirals to continuous therapy or to breaks lasting one, one, two, two, and three months,
If STIs are supposed to make life easier for people with HIV, they failed miserably in this study group.

These resistance findings suggest two lessons: Don’t interrupt (or don’t prescribe) a nonboosted PI regimen, and don’t interrupt any NNRTI regimen.

each followed by three months on therapy.

If STIs are supposed to make life easier for people with HIV, they failed miserably in this study group. Two thirds of those in the STI arm (66.5%) dropped out during the 24-month trial, compared with 19.4% in the steady-treatment group. People in the STI group had a 4.6 times higher risk of dropping out (95% CI 3.0 to 7.3) than people in the control arm.

Statistical analysis keyed to the primary end-point—a CD4 count above 500 cells/mm$^3$ at month 24—determined that these STIs were “not noninferior” to uninterrupted therapy. Translated from StatSpeak into English, that means these STIs were worse than steady therapy. But some would question a CD4 threshold of 500 cells/mm$^3$ as a primary endpoint in an STI trial because CD4s invariably ebb when people with HIV stop taking antiretrovirals.

The treatment arms did not differ when rated by the main virologic endpoint: just over 90% of both groups had a 24-month viral load below 400 copies/mL. And 24-month cumulative risk of virologic failure—defined as a viral load above 400 copies/mL at any time in the steady-therapy group and at any time on treatment in the STI group—stood at 24% in the control group and 26% in the STI group.

Resistance-related mutations piled up during each of the first four drug breaks. At the study’s end 38 of 136 people (27.9%) randomized to try STIs had at least one mutation. Nearly three quarters of the people randomized to an STI (72.8%) took a nonnucleoside reverse transcriptase inhibitor (NNRTI), and 20% of them came away with a mutation. But half of the interrupters taking a PI—and most took unboosted PIs—ended up with PI mutations. Picking up mutations raised the risk of virologic failure 2.6 times in this trial.

These resistance findings suggest two lessons: Don’t interrupt (or don’t prescribe) a nonboosted PI regimen, and don’t interrupt any NNRTI regimen. Palmisano and coworkers took the precaution of stopping the NNRTI a set number of days before stopping nucleosides in an attempt to avoid de facto NNRTI monotherapy as efavirenz (EFV) or NVP slowly clears from the body. The Window trial protocol (see preceding section) called for the same safeguard. But research convincingly shows high patient-to-patient variation in NNRTI clearance rates,$^{18,19}$ as well as persistence of EFV levels high enough to provoke resistance up to 21 days after some people stop that drug.$^{18}$ So stopping EFV seven days before stopping nucleosides may avert resistance in certain people, but not in others.

Multivariate analysis singled out two independent predictors of virologic failure in the Italian study—unboosted PI therapy and archived mutations in viral DNA at study entry. Palmisano suggested checking DNA for occult mutations before letting a person essay STIs, but she could not explain how those mutants got archived in people supposedly taking their first antiretrovirals. One must pick from three possibilities: Some people had unreported failures before signing up for the study; they got infected with resistant virus; or the mutations evolved by chance.

Palmisano reported no new AIDS diagnoses or deaths in this two-year study, though she did not detail the fates of the many study dropouts. She counted 14 “serious adverse events” in each treatment arm but attributed only one of them to antiretrovirals or the trial protocol—acute retroviral syndrome in one break taker.

Defining STI-related safety

After tracking 167 people who interrupted treatment for a median of 96 weeks, ACTG 5170 investigators concluded that stopping antiretrovirals is safe in people with a pretreatment CD4 nadir above 350 cells/mm$^3$ and with at least that many CD4s when treatment stops [abstract 101]. But you might hear a different conclusion if you could quiz the five people who died (four from heart disease), the 10 with a new diagnosis of herpes zoster (nine while off treatment), the 10 with bacterial

### Table 3. CD4 drops in SMART and Staccato: STI versus steady therapy

<table>
<thead>
<tr>
<th>CD4 changes</th>
<th>STI arm</th>
<th>Steady-therapy arm</th>
<th>Ratio STI/steady</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staccato</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;350 before retreatment (in STI arm)</td>
<td>39.5%</td>
<td>3.8%</td>
<td>10.4</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>&lt;350 12 weeks after retreatment</td>
<td>14.1%</td>
<td>3.1%</td>
<td>4.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SMART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient-years &lt;350 cells/mm$^3$</td>
<td>31.7%</td>
<td>8.1%</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Patient-years &lt;250 cells/mm$^3$</td>
<td>8.2%</td>
<td>1.7%</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Patient-years &lt;200 cells/mm$^3$</td>
<td>3.1%</td>
<td>0.8%</td>
<td>3.9</td>
<td></td>
</tr>
</tbody>
</table>

Sources: Ananworanich J et al, abstract 102; El-Sadr W et al, abstract 106LB.
infection (seven while off treatment), the six with hypertension (five while off treatment), the four with thrombocytopenia (all while off treatment), the four with candidiasis (two while off treatment), the three with mucosal herpes simplex (two while off treatment), the one with sensory neuropathy while off treatment, or the one with acute retroviral syndrome.

Daniel Skiest (Baystate Medical Center, Springfield, Massachusetts) and ACTG coworkers enrolled 167 people with a pretreatment nadir above 350 cells/mm$^3$ (median 436 cells/mm$^3$), current CD4 count above 350 cells/mm$^3$ (median 833 cells/mm$^3$, with 92% above 500 cells/mm$^3$), and a viral load below 55,000 copies/mL (median pretreatment load 26,611 copies/mL, with 71% below 50 copies/mL). They had taken antiretrovirals for a median of 4.5 years, and all said they wanted a drug holiday.

At the end of follow-up only 17 of 144 people who stayed in the study (11.8%) had a confirmed CD4 count at or below 250 cells/mm$^3$, which was part of a composite primary endpoint that also included a new AIDS “event,” death, or the need to resume therapy.

In this study group a nadir count below 400 cells/mm$^3$ raised the risk of reaching the primary endpoint 1.95 times ($P=0.02$), and a viral load above 400 copies/mL at study entry raised the risk 2.75 times ($P=0.02$). In a multivariate analysis a lower CD4 nadir and a viral load above 50 copies/mL at entry independently raised the risk of reaching the primary endpoint. A hefty majority of people starting antiretrovirals today—anywhere in the world—probably have sub-400-cell nadirs.

Fourteen people restarted the regimen they stopped, and five of them (36%) endured virologic failure, a sad result. Thirty-two people resumed treatment with antiretrovirals while off treatment, and five of them (36%) failed.

As Margolis, cochair of this study, writes in his CROI review, “the possibility that morbid events not classically associated with HIV infection occur at an increased rate in patients off [ART] is of potential concern, and worthy of further study.”

An STI try in children

If STIs make sense for anyone, they make sense for children. For a 44-year-old, the prospect of taking antiretrovirals for the rest of your life is not a happy one; for a four-year-old, the prospect is noxious. A nonrandomized trial mounted by William Borkowsky (New York University) and pediatric ACTG colleagues found that gradually lengthened STIs provoked immune responses in children, but at the cost of a dwindling CD4 percentage and, in three children (21%), resistance [abstract 19].

Borkowsky and the PACTG 1015 team enrolled 14 children whose viral loads lay below 400 copies/mL for more than one year and below 50 copies/mL when the study began. They started with a three-day STI, then added two days to each successive drug break. Three children dropped out of the trial for personal reasons, and one can imagine many “personal reasons” interfering with a complicated on-and-off protocol like this.

The good news is that median off-treatment viremia peaked at 26,667 copies/mL during cycle seven, then never rose above 10,000 copies/mL, even though subsequent STIs grew longer and longer. Among eight children who reached STI cycle 13, seven had at least a 10-fold rise in HIV-specific CD4 cells, and HIV-specific lymphoproliferative responses also improved.

Median CD8 percentage climbed from 24% to 29.5%, but median CD4 percentage dipped from 40.5% to 36.5%. Resistance mutations emerged in three children—the 3TC-provoked M184V in one, the PI mutation V82A in one, and M184V plus assorted PI mutations in the third.

These mixed early results with a complex strategy suggest much remains to be learned about crafting safe STIs for children.
without HIV.\textsuperscript{31} That heightened risk of renal failure dropped from a 4.62-fold elevation in the days before potent antiretroviral combos to a 2.82-fold elevation in 2003.

Klotman did find a 2-fold higher incidence of acute renal failure in 2003 than in 1995. Yet the incidence rose in both the HIV and non-HIV cohorts. And potent antiretrovirals promote longer survival of more people who also have diabetes and liver disease—both of which raised the risk of acute renal failure in Klotman’s 2003 cohort.

Despite fears that antiretroviral-riled liver enzymes would fuel an epidemic of liver disease in people with HIV, much research now shows that people with hepatitis virus infection do better with than without antiretrovirals.

The D:A:D team came to CROI with evidence indicting PIs—and perhaps exculpating NNRTIs—for boosting the MI risk, apparently by jacking up lipids [abstract 144]. But this work also charted a dwindling MI rate in the 23,437-person D:A:D cohort. And other research detailed at the conference failed to link PIs to a heightened risk of heart disease.

D:A:D embraces 11 cohorts from Australia, Europe, and the United States with follow-up through February 2005. All cohort members took a three-drug regimen including either a PI or an NNRTI, but median duration of PI therapy far exceeded that of NNRTI treatment (3.0 years versus 0.9 years). The median age of D:A:D members when they entered the cohort in 2000-2001 was 39 years (interquartile range [IQR] 34 to 45 years).

Through 94,469 person-years of follow-up, D:A:D tabulators counted 345 MIs for an incidence of 3.7 per 1,000 person-years. Stated another way, a researcher would have to monitor 1,000 antiretroviral-treated people for a year to count 3.7 heart attacks. Nina Friis-Møller (Copenhagen HIV Program) reported that MI risk in the cohorts dropped by half from 1997 through 2003-2004 (RR 0.50) — after statistical adjustment for demographic and cardiovascular risk factors as well as antiretroviral exposure.

When statisticians adjusted that analysis for the latest total cholesterol, “good” high-density lipoprotein (HDL) cholesterol, and triglycerides, the improvement in MI incidence vanished. That finding suggests that improving lipid profiles—perhaps because of switching from PIs to NNRTIs, taking antilipid drugs, or getting serious about diet and exercise — apparently circumvented the potential for an increased MI risk as the cohort aged. An earlier reckoning of D:A:D data showed a switch away from PIs to NNRTIs, a doubling in use of lipid lowerers (from 3.5% to 7.6%), a small drop in proportion of current smokers (from 47.4% to 45.0%), and a big jump in proportion of ex-smokers (from 16.0% to 24.7%) from 2000 to 2003.\textsuperscript{37}

The latest D:A:D analysis figured a 16%
The impact of individual antiretrovirals. And when D:A:D statisticians broke that down by drug class, they found a 16% higher MI risk with each year of PI therapy ($P = 0.0001$). Factoring lipid changes into that equation whittled the MI risk down to 10%. Risk of MI changed not at all with added years of NNRTI therapy, but Friis-Møller reminded attendees that the analysis rests on relatively fewer years of NNRTI therapy.

D:A:D’s math mavens also ran sensitivity analyses considering people who took PIs but never took an NNRTI, and people who tried an NNRTI but never tasted a PI. Once more, every 12 months of PI therapy inflated the MI risk 16%, while MI odds seemed to dwindle for each year of NNRTI treatment. Despite the cohort’s huge size, statisticians still can’t weigh the impact of individual antiretrovirals.

### Confirming trends in US cohorts

In a northern Californian cohort of men with HIV infection, every added year of PI therapy upped the age-adjusted MI risk by precisely the same factor recorded in D:A:D—1.16 [abstract 737]. But Daniel Klein (Kaiser Permanente, Hayward, California) reported that this uptick lacked statistical significance in his smaller cohort ($P = 0.112$) and that the risk may be easing in men taking PIs for the longest duration studied, six to 9.5 years (Table 4).

If PIs swell the risk of heart attacks, why would men taking them more than six years have fewer MIs and a lower relative risk than men taking them two to six years? The unsurprising answer mirrors D:A:D disclosures—people are smoking less, taking antilipid pills, and reining in high blood pressure. Also, people with bad PI-induced lipid profiles would probably not keep taking PIs year after year if they could switch to a non-PI combo or to the more lipid-friendly atazanavir (ATV).

From 2002 through 2005 the percentage of smokers among 5,430 HIV-infected men in Klein’s cohort dropped from 21.1% to 17.9%, and from 2000 to 2005 the percentage with systolic blood pressure above 140 mm Hg fell from 22.0% to 11.6%. The proportion of PI-treated men taking lipid-lowering agents rocketed from 1% in 1997 to 27% in 2005 ($P < 0.001$). And from 2003 through 2005 the percentage of PI takers using ATV climbed from 6% to 35% ($P < 0.001$). (But ritonavir [RTV]-boosted ATV does jack up cholesterol quotients in some children. See “Arteries and lipids in adults and kids,” below.)

Probably because of the moves toward ATV and lipid lowerers, 59.3% of the HIV cohort had total cholesterol below 200 mg/dL in 2004 to 2005 compared with 43.6% in 2000 to 2001. In that same period the percentage with HDL cholesterol above 39 mg/dL edged up from 47.5% to 52.2%.

Overall age-adjusted coronary heart disease (CHD) and MI rates remained significantly higher in men with HIV than in men without HIV (6.0 versus 2.9 CHD events per 1,000 person-years, $P < 0.001$; MI 3.6 versus 2.2 events per 1,000 person-years, $P = 0.002$). But the Framingham Risk Score for CHD among HIV-infected men actually eased from 2000-2001 to 2004-2005 (8.6% to 8.3%), even though the cohort grew significantly older ($P < 0.001$).

A second US cohort inquest, the HIV Outpatient Study (HOPS), confirmed the importance of traditional cardiovascular risk factors in people with HIV [abstract 735]. But this analysis by Kenneth Lichtenstein (University of Colorado, Denver) winked out no links between specific antiretrovirals or classes and CHD.

From 1993 through 2005 the HOPS team tallied 57 MIs, 22 strokes, 86 cases of coronary artery disease, and 22 cases of peripheral vascular disease in 8,024 people with HIV, most of them white men. Diagnoses of MI peaked at the turn of the millennium, then fell as cohort members started taking more antihypertensives and antilipid drugs. Incidence of MI among cohort members approached 3.5 per 1,000 person-years in 2000, remarkably close to the overall 3.7 incidence in D:A:D, then plunged to about 1.1 in 2005.

Multivariate analysis involving 1,807 people who sustained 57 cases of cardiovascular disease flushed out five independent predictors of heart disease:

- Age over 40 years: adjusted odds ratio (AOR) 3.31 ($P < 0.001$)
- Diabetes: AOR 3.24 ($P < 0.001$)
- Hyperlipidemia: AOR 1.95 ($P = 0.024$)
- Hypertension: AOR 1.73 ($P = 0.059$)
- Nadir HDL cholesterol: AOR 0.97 ($P = 0.004$)

Individual antiretrovirals, antiretroviral classes, and switches from older PIs to ATV or any NNRTI had no impact on the risk of cardiovascular disease. But among 363 people with hyperlipidemia, taking antilipid agents cut the risk of heart disease 66% (AOR 0.34, 95% CI 0.14 to 0.85, $P = 0.021$). In the high-lipid subset smoking upped the odds of heart disease 2.22 times ($P = 0.057$), age over 40 years made heart disease 2.38 times more likely ($P = 0.087$), and diabetes raised the risk 2.45 times ($P = 0.052$).

For now the bottom line from these three studies appears to be that PIs make MIs more likely. But D:A:D, the California study, and HOPS all strongly suggest that easing lipids and other traditional risk factors may wipe out the MI risk pinned on PIs.

### Arteries and lipids in adults and kids

The D:A:D data do level a serious indictment against PIs for promoting heart attacks in people with HIV, an indictment supported by earlier findings in the French Hospital Database. But the conviction remains in question, as other CROI studies (including the just-reviewed HOPS data) failed to turn up PI-incriminating evidence.

A three-year study of matched threesomes found no significant differences in carotid artery intima-media thickness (IMT)—an accepted marker of coronary artery atherosclerosis and cardiovascular disease—in HIV-infected people taking a PI, HIV-infected people who never took a PI, and people without HIV, reported Judith Currier (University of California, Los Angeles) [abstract 145]. But the PI takers did have moderately faster carotid wall thickening, and 61% of the PI group did not get a boost from RTV.
Earlier work by a different group found a 10 times higher IMT gain in 121 people with HIV after one year of follow-up than in 27 age- and gender-matched uninfected controls, and lower CD4 nadirs inflated the risk of thickening carotid walls.\textsuperscript{39} Another one-year study of 346 HIV-infected people graphed a slow but significant IMT increase but did not tie it to type or duration of ART.\textsuperscript{40} A third study of 233 people in the same HIV cohort traced a rise in median IMT during the first 12 months of ART, then a drop through 36 months of follow-up.\textsuperscript{41} In that time more people started taking lipid lowerers, stopped taking PIs, and stopped smoking. These Aquitaine cohort researchers posited a succinct conclusion: “The progression of atherosclerosis in HIV-infected patients can be controlled.”

Currier and ACTG 5078 colleagues matched 44 sets of three people for age, race, gender, blood pressure, smoking, and menopausal status. They excluded people with a history of MI, diabetes, or uncontrolled hypertension. Baseline IMT proved similar in the PI-treated, PI-naive, and HIV-uninfected sets and barely changed through 144 weeks of follow-up (Table 5).

Higher fasting blood sugar and fasting insulin did correlate with IMT in this analysis. Currier noted that the small size of the cohort and normal lipid levels among some PI-treated people may have diluted the study’s power to spot a difference between groups. So even if this trial does not completely vindicate PIs in promoting cardiovascular disease, it hints that PI therapy without lipid abnormalities may not pose a grievous threat to the heart.

A second and much larger case-control study did chart significantly thicker carotid walls in an HIV cohort than in a large cohort of healthy people not tested for HIV [abstract 738]. But this age and gender matching of 292 HIV-infected “cases” and 1,168 “controls” could not tie carotid IMT changes to any antiretroviral class regardless of carotid segment scanned, antiretroviral treatment duration, or statistical model.

The HIV cohort and the matched, prospectively tracked Carotid Atherosclerosis Progression Study group had grayed to a median age of 53.2 years, reported Christoph Stephan (JW Goethe University Hospital, Frankfurt). But the control group had a worse cardiovascular risk profile, with significantly higher body mass index, systolic and diastolic blood pressure, need for blood pressure medication, total cholesterol, and LDL cholesterol. More people with HIV took antilipid drugs (18.5\% versus 4.1\%, $P<0.0001$), and the HIV group averaged 27.0 cigarette pack-years compared with 13.4 in the control group ($P<0.0001$).

Because of the inability to correlate thicker carotid arteries—measured at six sites—to antiretroviral therapy, Stephan and colleagues blamed the worse IMT on HIV itself. Statisticians figured that the heightened IMT risk ratio in people with HIV made them four to five years older in “vascular age” than the control group and gave them a 4\% to 14\% higher risk of one “vascular event” in five years.

A single-center cross-sectional study of 132 people with HIV found two independent predictors of subclinical atherosclerosis defined by a carotid IMT above 0.8 mm or plaque detection—combination antiretroviral experience (OR 10.5, 95\% CI 2.8 to 39) and a 10-year coronary risk at or above 10\% (OR 4.2, 95\% CI 1.5 to 12).\textsuperscript{42}

The study included 93 people taking antiretrovirals and only 39 treatment-naive people, 32 of whom (82\%) earned a very low-risk rating on the Framingham scale (10-year coronary risk below 5\%). Besides consisting predominantly of antiretroviral-treated people, the group with subclinical carotid atherosclerosis was the oldest, had the lowest CD4 counts, had the highest HIV duration and the highest Framingham risk scores, and had abnormal fat distribution. So independent scrutiny of the statistical methods might prove worthwhile.

Children with HIV also have thicker carotid walls than uninfected children, according to results of a small, single-center, case-control study by Grace McComsey (Rainbow Babies and Children’s Hospital, Cleveland). Besides having higher carotid IMTs, children with HIV

\begin{table}[h]
\centering
\caption{Mean change in carotid IMT in three groups}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Group & Baseline (mm) & Week 72 (mm) & Week 144 (mm) & IMT change (mm/year) & \(P\) \\
\hline
PI group & 0.693 & 0.715 & 0.744 & 0.0102 & 0.19\textsuperscript{*} \\
PI-naive & 0.711 & 0.686 & 0.740 & 0.0047 & 0.78\textsuperscript{†} \\
HIV-Uninfected & 0.690 & 0.714 & 0.725 & 0.0083 & 0.71\textsuperscript{‡} \\
\hline
\end{tabular}
\end{table}

\textsuperscript{*}PI-treated versus PI-naive.
\textsuperscript{†}PI-naive versus HIV-uninfected group.
\textsuperscript{‡}Combined HIV groups versus HIV-uninfected group.

Despite generally good lipid reports in adults starting or switching to ATV, some US and South African children taking RTV-boosted ATV saw cholesterol readings climb toward the danger zone...
had higher levels of myeloperoxidase (a cardiovascular risk surrogate) and higher lipids than did controls without HIV [abstract 691]. The analysis involved 27 children with HIV and 17 age-, gender-, race-, and weight-matched controls. The HIV-infected children were all taking a stable regimen, 52% with an NNRTI, 41% with a boosted PI, and 7% with both an NNRTI and a boosted PI. Eighteen children in the HIV group were girls, and 18 were African American. The study excluded children with a family history of diabetes or premature cardiovascular disease.

Median myeloperoxidase proved significantly higher in the HIV group (1.299 versus 746 pmol/L, P = 0.01), and median C-reactive protein, another heart risk factor, was nonsignificantly higher in the children with HIV (0.67 versus 0.43 mg/L, P = 0.15). The HIV group also had significantly higher fasting total cholesterol, non-HDL cholesterol, and triglycerides than did controls.

Common carotid IMT was comparable in the two groups, but median left internal carotid artery IMT was significantly higher in children with HIV (0.50 versus 0.45 mm, P = 0.038). The HIV group also had a higher median right internal carotid artery IMT, but that difference fell shy of statistical significance (0.50 versus 0.45 mm, P = 0.08).

An earlier, similarly small case-control study in France found no greater carotid IMT in children with HIV than in those without HIV.26 None of the vascular variables measured—IMT, endothelium-dependent dilation, and endothelium-independent dilation—differed between 34 children taking antiretrovirals and 15 treatment-naive children with HIV. So HIV’s impact on children’s arteries remains an open question. Answers may come from McComsey’s planned 144-week follow-up of her study group.

José Ramos (Hospital 12 de Octubre, Madrid) and colleagues at other Spanish hospitals reported a significant jump in high cholesterol rates (more than 200 mg/dL) in 91 children starting a PI—from 9% before treatment to 48% after 24 months (P < 0.01) [abstract 690]. The biggest cholesterol gains (93.5 mg/dL after 24 months) came in seven children starting lopinavir/ritonavir (LPV/r). Among 15 children starting an NNRTI, 13% had high cholesterol before treatment and 10% after 24 months. Proportions of children with triglycerides above 170 mg/dL did not rise significantly through 24 months of PI or NNRTI therapy. Taller and heavier children, and those with a viral load above 100,000 copies/mL, ran a higher risk of hypercholesterolemia.

Despite generally good lipid reports in adults starting or switching to ATV, some US and South African children taking RTV-boosted ATV saw cholesterol readings climb toward the danger zone, reported Grace Aldrovandi (Children’s Hospital of Los Angeles, California) and PACTG 1020A colleagues [abstract 689]. Total cholesterol rose from below to above 180 mg/dL in eight of 81 children (10%) after 24 weeks of ATV/r and in eight of 48 (17%) after 48 weeks. Three of 82 children (4%) wound up with cholesterol readings above 200 mg/dL at week 24, as did four of 49 (8%) at week 48. Aldrovandi traced a significant correlation between RTV boosting and higher cholesterol at weeks 24 (P = 0.01) and 48 (P = 0.03). Unfasted triglyceride levels rose nonsignificantly.

One more SMART surprise
One in 10 people enrolled in the SMART treatment interruption trial has asymptomatic ischemic heart disease [abstract 736]. But PI therapy or longer antiretroviral therapy did not swell that risk. Longer NNRTI treatment appeared to lower the risk of asymptomatic ischemic heart disease compared with no NNRTI experience.

Those findings emerged from a 3,456-person analysis of SMART enrollees with an electrocardiogram (ECG) and without evidence of earlier heart disease. Their age averaged 46 years, one third were black, and they had taken antiretrovirals for an average six years. Only 5.3% had never tried antiretrovirals, 32.2% never sampled a PI, and 36.4% claimed NNRTI naïveté. Everyone had a CD4 count above 350 cells/mm³, and 66.7% had a viral load under 400 copies/mL. Average total cholesterol stood below the danger zone at 193 mg/dL (4.99 mmol/L), but the group’s average HDL cholesterol was low (43 mg/dL, 1.12 mmol/L), and their triglycerides were high (231 mg/dL, 2.59 mmol/L).

Andrew Carr (St. Vincent’s Hospital, Sydney) reported that 10.1% had ECG evidence of asymptomatic ischemic heart disease—Q waves and/or ST depression. In contrast, only 1.5% had symptomatic ischemic heart disease. Carr tallied 2.1% with arrhythmias and 1.4% with left ventricular hypertrophy.

Neither gender, race, smoking, nor antilipid therapy swayed the risk of asymptomatic ischemic heart disease, but four factors did—older age, current antihypertensive therapy, diabetes, and one to three years of NNRTI experience, the last of which lowered the risk (Table 6). Carr and SMART colleagues figure that current antihypertensive therapy reflects long-standing hypertension. Current lipid levels may not have nudge the risk equation, they speculate, because lifelong lipid levels may “have changed recently with [ART] (95% of patients) and/or lipid-lowering therapy (15%), so altering any association between lipid levels and ischemic heart disease.”

These are interim data, Carr noted. The SMART team plans to analyze asymptomatic ischemic heart disease risk in another 1,000 trial participants.

But why would ischemia threaten people with HIV infection if antiretrovirals can’t be blamed or—in the case of NNRTIs—may actually lower the risk? The HIV literature is pregnant with one potential risks of HIV itself—despite the cardiovascular threat posed by ART eclipsed the potential risks of HIV itself—despite a steady stream of research in cells, animals, and humans.
Sizing up endothelial function is one way to get a fix on cardiovascular health. As observed by David Nolan and Simon Mallal (Royal Perth Hospital, Perth, Australia), “endothelial dysfunction is an early phase of atherogenesis in which the vasodilatory properties of the endothelium are diminished, preceding the development of atherosclerotic plaque in the arterial wall.” Cell studies link HIV’s gp120 protein and Tat protein to endothelial damage, while gp120 incites killing of neonatal rat ventricular myocytes and human coronary artery endothelial cells. Tat and the inflammatory cytokine TNF-alpha apparently team up to help leukocytes stick to endothelial cells. Mice genetically jogged so their cells express HIV-1 nef get heart disease.

What does HIV do to human endothelium still inside humans? You can get a good noninvasive guess by mapping flow-mediated dilation of the brachial artery. A study comparing 22 PI-treated people and 15 PI-naive people with HIV linked PI therapy to high triglycerides and triglyceride-rich lipoproteins, then tied those changes to impaired endothelial function. Nolan’s study suggested preserved endothelial function in people with advanced infection.

But a more recent prospective case-control study in Israel charted an inverse correlation between viral load and endothelial dysfunction—the higher the load, the worse the dysfunction (P < 0.005). That finding bolsters the idea that infection—especially an infection left uncontrolled for years, or intermittently controlled as treatment stops and starts—is bad for the heart. As the Israeli researchers note, endothelial dysfunction, hypercoagulability, hypertriglyceridermia, and abnormal coronary artery pathology plagued people with HIV infection long before they started taking PIs. But as results of these three studies suggest, no one can say for sure whether PIs or HIV is tougher on endothelial cells.

At the 13th CROI, Priscilla Hsue (San Francisco General Hospital) offered evidence that atherosclerotic progression to heart disease in people with HIV may involve the infected person’s ongoing struggle not only with HIV, but also with CMV [abstract 741]. Almost everyone who reaches the age of sexual consent—and then consents—has CMV. People with a working immune system, including most people taking ART, keep CMV under control by directing CMV-specific T cells against the virus. But what does that ever-smoldering inflammatory battle against CMV do to the circulatory system?

Because CMV apparently hastens atherosclerosis in heart transplant patients, and because HIV infection upsets CMV-specific immunity, Hsue hypothesized that immune responses to this herpesvirus may explain faster atherosclerosis in people with HIV. To explore this possibility, she mounted a case-control study of 93 people with HIV and 37 uninfected controls, then gauged carotid IMT in 12 predefined segments. People with HIV had to be on a stable antiretroviral regimen for at least a year (and 92% were) or taking no antiretrovirals. Median CD4 count in the HIV group measured 354 cells/mm³, and 57% had an HIV load under 75 copies/mL.

Compared with controls, the HIV-infected group had higher proportions of smokers (42% versus 19%, P = 0.03) and people with hypertension (30% versus 11%, P = 0.03). Controls had significantly higher HDL and LDL cholesterol, while people with HIV had significantly higher triglycerides.

Median carotid IMT proved significantly greater in the people with HIV (0.95 mm) than in controls (0.68 mm) (P < 0.001), a finding confirming results of Hsue’s earlier IMT study. After statistical adjustment for other cardiovascular risk factors, the HIV group averaged 27% thicker carotid walls than the non-HIV controls (P < 0.001). People with HIV also had significantly higher median levels of C-reactive protein (CRP), a heart disease marker, than did controls (1.1 versus 0.8 mg/L, P = 0.05). But neither traditional nor HIV-

### Table 6. Independent risk factors of asymptomatic IHD in SMART

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 50 to 59 years (vs &lt;40 years)</td>
<td>1.5</td>
<td>1.1 to 2.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Age &gt;60 years (vs &lt;40 years)</td>
<td>2.1</td>
<td>1.4 to 3.3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Current antihypertensive therapy</td>
<td>1.5</td>
<td>1.1 to 2.0</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>NNRTI therapy 1 to &lt;3 years (vs NNRTI naive)</td>
<td>0.7</td>
<td>0.5 to 1.0</td>
<td>0.09</td>
</tr>
</tbody>
</table>

IHD = ischemic heart disease.

Source: Carr A et al, abstract 736.
specific cardiovascular risk factors correlated with CRP readings.

CD4- and CD8-cell activation proved significantly higher in the HIV group ($P<0.001$ for both), but neither variable predicted carotid IMT. On the other hand, every 10-fold jump in percent of CMV-specific CD8 cells meant an average 14% rise in carotid IMT ($P<0.001$). When Hsue adjusted that analysis for other cardiovascular risk factors, every 10-fold increment in CMV-specific CD8s still correlated with a 9% upswing in carotid IMT ($P<0.001$). Similar correlations held true for CMV-specific CD4 cells and waxing IMT.

“Taken together,” Hsue concluded, “these findings suggest that the accelerated atherosclerosis in HIV disease may be mediated by an increased inflammatory response that is directed against CMV.”

But does that finding contradict the assumption that controlling HIV with antiretrovirals is enough to stop progression to atherosclerosis? Hsue did not distinguish between virologic responders and nonresponders in her analysis. And she told the IAPAC Monthly this line of research has a way to go before answering that question.

It’s the virus, moron?

Results from the 13th CROI’s core antiretroviral studies—SMART, D:A:D, the IMT studies, and others—resist packaging in a tidy take-home bundle. But the conference surely ranks among the most productive in recent memory and sent most attendees home with fresh perspectives on how best to prescribe antiretrovirals.

Starkly refutatory results like SMART’s invariably inspire the unhelpful bromide that new findings raise more questions than they answer. Even when that cliché proves true, ducking behind it does not excuse clinicians from answering whatever questions they can.

SMART, for example, is hardly the first study to find that lack of antiretroviral therapy may pose a bigger threat of organ damage than taking these imperfect drugs day after day. In all the talk on this seminal study—at least all the talk this reporter heard—no one mentioned the 9th CROI study of Samuel Bozzette (University of California, San Diego) showing that heart disease and stroke admissions to Veterans Administration (VA) hospitals fell by half as HIV-infected vets took ever-more-potent antiretroviral combinations.57

And swallowing PI or NNRTI regimens for four or more years sent no more people to the hospital for heart trouble or stroke than taking those combinations for four, three, or two years. The risk of admission for cardiovascular or cerebrovascular disease slipped 21% for people taking PIs more than 24 months versus not at all, though that improvement lacked statistical significance. From 1995 although 2001, as PI and NNRTI regimens became routine, all-cause mortality plunged from 21.3 to 5.0 deaths per 100 patient-years.

Bozzette’s conclusion back in 2002 sounds sounder than ever today: “Fear of accelerated vascular disease should not deter patients and providers from using the highest-quality care for HIV, as defined by the use of combination [ART] that is compatible with current guidelines.”

Not long after Bozzette published the VA study, other US researchers reported that severe clinical complications—“grade 4 events” like liver and heart disease—had become more common than new AIDS diagnoses among 2,947 people taking potent regimens in clinical trials (11.4 versus 5.6 per 100 person-years).58 That finding fanned fears that triple therapy with PIs or NNRTIs caused these new complications.

Now it appears that fear got overblown. As Bozzette explained in a recent e-mail, “many of the newer complications that came with HAART were attributed to PIs or NNRTIs because they came together.” But people forgot to factor in the “huge increase” in NRTI use around the same time and the much longer survival of people with HIV infection.

The latest big cohort studies confirm the end-organ-protecting prowess of strong antiretrovirals. In a just-published 22-cohort Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) analysis of 7,680 people with HIV, for example, mortality from organ failure dropped by more than half after potent combinations arrived, from 1.0% to 0.4%.59 Meanwhile, the death rate from non-AIDS infections fell from 8% in the 15 years after HIV seroconversion in pre-1997 cohort members to 3% in more recent years. And what about classic AIDS-defining infections? Of course they kill many fewer people today than they did before 1997. But CASCADE researchers found that classic OIs remain the leading cause of death of people with HIV—and a real good reason to take ART.

When viewed from this perspective, SMART’s finding that people who interrupt antiretrovirals run a higher risk of disease progression and death—from AIDS and “non-AIDS” causes—than people who keep taking their drugs sounds as intuitive as can be.

And how does Bozzette put these pieces together?

“I know this sounds moronic,” he told the IAPAC Monthly, “but my reaction is that HIV is a bad virus that should not go unchecked. I cannot imagine that we would not suppress from day one of care if we could.”

Mark Mascolini writes about HIV infection (markmascolini@earthlink.net).

References
HAART in low-income settings had lower CD4 cell counts (median 108 cells/µL versus 234 cells per µL), were more likely to be female (51% versus 25%), and more likely to start treatment with a non-nucleoside reverse transcriptase inhibitor (NNRTI) (70% versus 23%). At six months, the median number of CD4 cells gained (106 cells/µL versus 103 cells/µL) and the percentage of patients reaching HIV-1 RNA levels lower than 500 copies/mL (76% versus 79%) were similar. Mortality was higher in low-income settings (124 deaths during 2,236 person-years of follow-up) than in high-income settings (414 deaths during 20,532 person-years). The adjusted hazard ratio (HR) of mortality comparing low-income with high-income settings fell from 4.3 (95% confidence interval [CI] 1.6-11.8) during the first month to 1.5 (0.7-3.0) during months seven to 12 months. The provision of treatment free of charge in low-income settings was associated with lower mortality (adjusted HR 0.23; 95% CI 0.08-0.61).

INTERPRETATION: Patients starting HAART in resource-poor settings have increased mortality rates in the first months on therapy, compared with those in developed countries. Timely diagnosis and assessment of treatment eligibility, coupled with free provision of HAART, might reduce this excess mortality.


Clinical Infectious Diseases

Distribution of health care expenditures for HIV-infected patients

Chen RY, Accott NA, Westfall AO et al.

BACKGROUND: Health care expenditures for persons infected with human immunodeficiency virus (HIV) in the United States determined on the basis of actual health care use have not been reported in the era of highly active antiretroviral therapy (HAART).

METHODS: Patients receiving primary care at the University of Alabama at Birmingham HIV clinic were included in the study. All encounters (except emergency room visits) that occurred within the University of Alabama at Birmingham Hospital System from March 1, 2000, to March 1, 2001, were analyzed. Medication expenditures were determined on the basis of 2001 average wholesale price. Hospitalization expenditures were determined on the basis of 2001 Medicare diagnostic related group reimbursement rates. Clinic expenditures were determined on the basis of 2001 Medicare current procedural terminology reimbursement rates. RESULTS: Among the 635 patients, total annual expenditures for patients with CD4 counts <50 cells/mL (US$36,533 per patient) were 2.6 times greater than total annual expenditures for patients with CD4 counts ≥50 cells/mL (US$13,885 per patient), primarily because of increased expenditures for non-antiretroviral medication and hospitalization. Expenditures for HAART were relatively constant at approximately US$10,500 per patient per year across CD4 count strata. Outpatient expenditures were US$1,558 per patient per year; however, the clinic and physician component of these expenditures represented only US$339 per patient per year, or 2% of annual expenses. Health care expenditures for patients with HIV infection increased substantially for those with more advanced disease and were driven predominantly by medication costs (which accounted for 71% to 84% of annual expenses). CONCLUSIONS: Physician reimbursements, even with 100% billing and collections, are inadequate to support the activities of most clinics providing HIV care. These findings have important implications for the continued support of HIV treatment programs in the United States.

DECADE OF HAART
HISTORICAL PERSPECTIVES
AND FUTURE DIRECTIONS

September 25-26, 2006 — San Francisco

On the decade anniversary of HAART, the International Association of Physicians in AIDS Care (IAPAC) is convening an historic meeting to review our collective progress, discuss obstacles faced and overcome, lessons learned, and challenges that lie ahead. Registration is limited. Visit www.iapac.org to view the meeting program and to register online!
### Co-Chairs

| John G. Bartlett, MD | Joep MA Lange, MD, PhD |

### Featured Speakers*

<table>
<thead>
<tr>
<th>Samuel Bozzette</th>
<th>David A. Cooper</th>
<th>Martin Delaney</th>
<th>Anthony Fauci</th>
</tr>
</thead>
<tbody>
<tr>
<td>José M. Gatell</td>
<td>Brian Gazzard</td>
<td>Diane Havlir</td>
<td>Christine Katlama</td>
</tr>
<tr>
<td>Jens D. Lundgren</td>
<td>John W. Mellors</td>
<td>Julio SG Montaner</td>
<td>Graeme Moyle</td>
</tr>
<tr>
<td>Paul Palumbo</td>
<td>John Phair</td>
<td>Jürgen Rockstroh</td>
<td>Mark Wainberg</td>
</tr>
</tbody>
</table>

*Visit www.iapac.org to view the complete faculty roster.

This activity is jointly sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ) and International Association of Physicians in AIDS Care (IAPAC), and has been approved for 18.0 AMA PRA Category 1 Credits™.
There is no strong association between long-term use of antiretroviral therapy (ART) and death from liver disease, according to a study presented at the 13th Conference on Opportunistic Infections and Retroviruses (CROI) held February 5-8, 2006, in Denver. However, when the researchers controlled for the beneficial effects ART has on CD4 counts, they found that there was some evidence that ART use in the longer term was associated with an increased risk of liver disease. Importantly, the international team of researchers also found that low CD4 count, coinfection with hepatitis B virus (HBV) or hepatitis C virus (HCV), and age are the main risk factors for death from liver-related disease among HIV-positive patients on ART for up to seven years.

There has been concern that extended use of ART may be associated with a risk of impaired liver function or liver-related death, particularly for patients who are HBV- or HCV-coinfected. Accordingly, researchers from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study prospectively gathered data on 23,441 patients and calculated the rate of liver-related death according to the number of years of exposure to ART. The researchers also looked at the risk factors for liver-related death (Figure 1).

Just under 77,000 person-years of follow-up were available for the analysis. A total of 1,248 patients died, with 183 deaths (15%) attributed to liver-related causes. Of the patients who died because of liver disease, 17% had active HBV, 66% had HCV, and 7% were coinfected with both. The median duration of use of ART among patients dying of liver disease was three years.

The researchers then looked at the independent risk factors for death from liver disease. These were a low baseline CD4 count (risk ratio [RR], 1.18); older age (RR, 1.34); injecting drug use (RR, 2.49); HBV coinfection (RR, 2.31); and HCV coinfection (RR, 7.30).

When the researchers looked at the rate of liver-related death according to the length of ART exposure, they failed to find any significant association. However, when they adjusted these results for CD4 count at the time of death—therefore taking into account the beneficial effects of ART on immune function—a significant association emerged (P = 0.03). They cautioned, however, that further data were required before firm conclusions could be drawn and concluded that the main risk factors for liver-related death were “low CD4 counts, chronic coinfection with [HBV]/[HCV] and age.”

Reference

Editor’s Note: Reprinted with permission from www.aidsmap.com (first e-published February 21, 2006).

Long-term ART and liver-related death
What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
1) If you believe in making a change and want to, you have a voice (to do so). 2) It is not how much we do, but how much love we put into doing it.

What activities, avocations, or hobbies interest you?
Do you have a hidden talent?
Beadwork (beaded jewelry).

If you could live anywhere in the world, where would it be?
In the Bahamas.

Who are your mentors or real life heroes?
Nelson Mandela.

With what historical figure do you most identify?
I do not so much identify with but admire Mahatma Gandhi, the Indian spiritual leader, statesman, and human rights activist.

Who are your favorite authors, painters, and/or composers?
I don't have a favorite author but I have just read and enjoyed Long Walk to Freedom by Nelson Mandela, and The Da Vinci Code by Dan Brown.

If you could have chosen to live during any time period in human history, which would it be?
Ancient Egypt.

If you did not have the option of becoming a physician, what would you have likely become, given the opportunity?
A singer/songwriter.

In your opinion, what are the greatest achievements and failures of humanity?
Greatest achievement: Sliced bread. Greatest failures: Wars.

What is your prediction as to the future of our planet one full decade from present day?
The world will be a better place than it is now, with fewer diseases and less poverty.
People infected with HIV through unsafe practices at government clinics have routinely been denied medical treatment and compensation. Now they can’t even tell their story to policymakers who might be able to help.

Brad Adams, Director of Human Rights Watch in Asia, quoted in a March 11, 2006, Agence France-Presse report detailing the group’s account of the house arrest of 23 HIV-positive Chinese patients. Adams stated that China had placed the patients under house arrest to stop them from traveling to Beijing to seek redress during the annual National People’s Congress meeting, scheduled to be held March 5-14, 2006. All 23 patients are from the Henan province, where a government-sanctioned blood-buying scheme in the 1990s left thousands infected with HIV.

Reluctantly [the doctor] agreed to give her a bed, but a few hours later he discharged her... even though she was becoming weaker and weaker. After going to several hospitals we got a bed at the Divina Providência Hospital, but she had become tired of being rejected and two days later she died.

Felisberta Massango, an activist with the Acção Humana, an Angolan nongovernmental organization, quoted in a March 23, 2006, IRIN PlusNews report relating how HIV-positive patients in Angola face stigma and discrimination not only from their relatives, friends, or neighbors, but also from health professionals who do not know enough about HIV/AIDS. She recently took her friend, who was already in the terminal stage of AIDS, to a public hospital in the Angolan capital, Luanda. According to Massango, her friend required hospitalization, but the physician on duty would not admit her and instead referred her to the Esperança Hospital, which specializes in treating people living with HIV/AIDS but is an outpatient facility operating only during the day. After much persuading, Massango’s friend was eventually admitted but died two days later.

It is a cruel irony that although this drug with no need for refrigeration seems to have been designed for places like Nigeria, it is not available here.

Helen Bygrave, a physician working in a Médecins Sans Frontières (MSF) AIDS treatment program in Lagos, Nigeria, in a March 15, 2006, Reuters report about that organization’s call for Abbott Laboratories to make its new formulation of Kaletra (lopinavir/ritonavir [LPV/RTV]) available to HIV-positive patients in developing countries, especially Africa. The new formulation is available in tablet form, does not require refrigeration, and has no dietary restrictions; all these traits make the drug a desirable addition to developing country pharmacies. MSF called for Abbott Laboratories to register the new formulation in less-developed countries, charge less than US$500 per patient per year, and remove patent barriers, allowing manufacture of generic versions of the drug.

From my own personal experience, there’s nothing more troubling, hopeless, and helpless than to watch someone you love die of AIDS.

Nancy Freudenthal, wife of Wyoming Gov. Dave Freudenthal, in a March 11, 2006, Associated Press report describing federal legislation sponsored by US Sen. Mike Enzi that would increase funding for HIV/AIDS treatment and prevention in rural areas of the United States. Enzi stated that the bill would also provide additional funds for HIV/AIDS treatment in minority communities. The state has identified 197 HIV-positive people living in Wyoming, 81 of whom are enrolled in the Ryan White CARE Act program. According to Sharon Renter, Chief of the Communicable Disease Section of the Wyoming Department of Health, the federal government only supplies enough funds to provide assistance to HIV-positive patients for four months each year. The rest of the funds have been provided by the state.

If they were HIV-positive from birth, they wouldn’t survive to this age.

Reverend Terry Charlton, a Roman Catholic priest and founder of St. Aloysius Gonzaga High School in Nairobi, Kenya, in a March 14, 2006, Chicago Sun-Times article about the school. The school, which enrolled 196 students this year, is tuition-free, and provides education solely to AIDS orphans; none of the students enrolled in the school are HIV-positive, but each has lost at least one parent to AIDS. The school opened its doors in 2003 with US$20,000 provided by the Chicago Province of Jesuits for operating costs. The school can currently accept only about half its applicants, and is trying to raise about US$1 million to construct a permanent building.