Rethinking STIs,
REVAMPING SALVAGE,
REVISITING TOXICITY
(or, the clouds
of chronicity)
Rethinking STIs, revamping salvage, revisiting toxicity
(or, the clouds of chronicity)

Mark Mascolini

Maybe the most notable finding of ACTG A5086 is that almost no one showed up for this presalvage trial of structured treatment interruptions. For those who did, the STI didn’t work. Again. But two other studies of treatment breaks at the 11th Conference on Retroviruses and Opportunistic Infections suggested where the strategy may make most sense—in children facing a lifetime of antiretrovirals.
José M. Zuniga

I purchased tickets last night to the new revival of playwright/person living with AIDS/AIDS activist Larry Kramer’s “The Normal Heart,” which opened last month in New York almost 19 years after it was first produced there to dramatize an epidemic which at that time had only recently come to be known by the acronym “AIDS.” I plan to see this autobiographical play during an upcoming visit to New York, in large measure to remember those whom I have lost to this insidious disease, and in part to commemorate the legacy of so many unnamed heroes in the 20-plus year battle in which we are collectively engaged.

Heroes are plenty in “The Normal Heart.” Kramer’s alter ego, Ned Weeks, directs his rage against both the US government and the gay community for ignoring what was then still commonly referred to as the “gay plague” and founds ACT UP, which is today credited with focusing attention on the AIDS epidemic in the United States. Joining him is Felix Turner, a high-profile (and closeted) writer at the New York Times who, while frustrating Ned, also provides an emotional link to the plague (Felix ultimately succumbs to AIDS). We have Ned’s friends—and fictional co-founders of the country’s first AIDS service organization, Gay Men’s Health Crisis (GMHC)—Bruce Niles, Mickey Marcus, and Tommy Boatwright. And, there is Emma Brookner, a physician who amidst her dying patients is slowly amassing information and urging others to spread the word. These heroes did not act in the face of uncertainty because of a desire for recognition— theirs was humility of spirit strengthened by a resolve to do right by their fellow man.

Life does not stray so much from art. Like Ned, Felix, Bruce, Mickey, Tommy, and Emma, there are countless heroes—named and unnamed—whose stories create the tapestry that is the AIDS pandemic’s history. In my years at the International Association of Physicians in AIDS Care (IAPAC), I have been blessed to meet so many of you who day in and day out reflect a remarkable heroism—a heroism bred from a struggle, certainly against disease, but most importantly, against the devastation it creates in the lives of so many men, women, and children around the world.

I was reminded of the need for heroes in our movement (and of the reality that so many will go unnamed and, though they do not seek glory, regrettably unrecognized) earlier this year as the IAPAC Board of Trustees and I fielded nominations for our annual Honoring Our Heroes awards. This year’s ceremony—which is scheduled to take place November 1, 2004, in Washington, DC—will recognize remarkable individuals, a non-profit consortium, and one corporation for making a measurable difference in the lives of people living with and affected by HIV/AIDS (see sidebar, “2004 IAPAC honorees”). Among them is Bono, a megastar who has for years now wielded his celebrity to advocate the AIDS and debt forgiveness causes. In one sentence contained in his acceptance letter to IAPAC, Bono summed up my feelings about the heroes—named and unnamed—that we are blessed to count among us—“I feel unworthy.” I am sure you will agree that is not the case, but it is that sentiment of acting for the good of others rather than for personal recognition that embodies the spirit of commitment that IAPAC is honored to recognize.

José M. Zuniga is President/CEO of the International Association of Physicians in AIDS Care (IAPAC), and Editor-in-Chief of the IAPAC Monthly.
t is the best of times, it is the worst of times,” International Association of Physicians in AIDS Care (IAPAC) President/CEO José M. Zuniga said in opening an April 6, 2004, summit on the pharmacoeconomics of AIDS drug access in the United States. Hosted by IAPAC, the one-day summit focused on the economics and ethics of “assured sustainability” of access to care and treatment for HIV in the United States which, according to Zuniga, will require “a mixed basket” of responses at a time when both the public and private sectors are experiencing severe economic constraints.

On the domestic front, the US$4 billion spent overall in the United States this year on antiretroviral drugs has slashed the rate of death and dramatically improved the quality of life for most HIV-positive patients. But the growing antiretroviral drug armamentarium and number of patients in need have far outstripped increases in funding, and systems of care are struggling to meet the challenge.

The most visible deficiency is with the AIDS Drug Assistance Program (ADAP), the public source of assistance for HIV-positive patients who are either uninsured or underinsured for their antiretroviral drug prescriptions. The National Alliance of State and Territorial AIDS Directors (NASTAD) announced the day after IAPAC’s summit that more than 1,200 patients in the United States find themselves on ADAP waiting lists. And that masks even greater numbers of patients who have been excluded through tightened eligibility standards and extended application procedures. People living with HIV/AIDS have not been able to gain access to drugs that they need because of restrictions placed on drug formularies or total numbers of prescriptions, increased co-payments, and lower caps on total benefits.

What is at the heart of this burgeoning crisis? Central to the daylong discussion at IAPAC’s summit in Washington, DC, were ways to address two main causative factors: the lack of adequate funding for ADAPs, as well as the rising cost of antiretroviral drugs.

There have been two significant flashpoints that have raised alarm among AIDS advocates, including HIV/AIDS-treating physicians. One flashpoint was in January 2004, when NASTAD announced that 15 states had implemented ADAP waiting lists—at the time that meant a little over 700 patients were affected. That number has steadily increased. The other flashpoint was in December 2003, when Abbott Laboratories hiked the price of its protease inhibitor, ritonavir, by 400 percent. Although the company eventually announced price concessions for all but private health insurers, the issue of antiretroviral drug pricing has become a catalyzing one within the AIDS advocacy community.

“This is not about blaming industry for the entirety of the problem,” Zuniga said, though issues of pricing remain an important part of the ongoing dialogue.

Joshua P. Cohen, an economist at the Tufts Center for the Study of Drug Development, said, for all of the complaints about the rising cost of drugs in the United States, only 10 percent of the healthcare dollar goes toward prescription drugs.

While that percentage is significantly higher with HIV care, there also is no doubt that those drugs have been responsible for slashing the number of AIDS deaths from their peak a decade ago, and dramatically increasing the quality of life for most HIV-positive patients.

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Rethinking STIs,

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robably the most encouraging result of AIDS Clinical Trials Group (ACTG) protocol A5086 came not from the data gleaned in this structured treatment interruption (STI) trial, but in its failure to meet a recruitment goal of 140 people [abstract 58]. The dispiriting outcomes of most earlier STI studies, suggested Constance Benson (University of Colorado, Denver), apparently sapped enthusiasm for this strategy among people with lots of treatment experience—and among the researchers themselves. So the ACTG halted enrollment at 41, only 29 percent of the target.

With a growing array of salvage options—and a few new products in the pipeline—many people with thick treatment histories apparently prefer moving straight to a new regimen rather than waiting for weeks or months in the hope that drug-susceptible virus will crowd out resistant mutants. That so-called reversion to wild-type virus has done little to foster better responses in most trials, and it didn’t work in ACTG A5086 either.

The ACTG trial was not the only testament to STI failings at the 11th Conference on Retroviruses and Opportunistic Infections (11th CROI). An Italian trial logged growing resistance rates in people following an off-and-on schedule, while two other studies linked brief treatment breaks to virologic failure or death. Three studies found little ground for optimism about STIs after treatment of primary infection, and treating infected infants soon after birth did not turn off the tap filling latent viral reservoirs. But three small trials testing new wrinkles in STIology met with some success. Two other small studies suggested that some children with chronic infection may safely suspend therapy.

New tactics—and new drugs—for rescue and salvage therapy won some notice at this CROI, while a deluge of new data swamped attendees with fresh details on antiretroviral side effects. This article ends with three studies on hemoglobin as a predictor of progression or survival in people with HIV, the continuing emergence of "non-AIDS cancers," promising results of surgery in people with HIV, and the first report on HIV trends and treatment in China’s Henan province, where thousands picked up HIV in a blood-selling scheme.
The most common mutations were M184V in 16 percent resistant virus appear at least once during a drug holiday. They had a median pretreatment CD4 count of 394 cells/mm\(^3\). They had taken their regimen for a median of 27 months and whom had finished four cycles of intermittent therapy. Looked for resistance in 136 people in the STI arm, 80 of 156 took drug breaks lasting one, one, two, two, and three months broken up by three-month stretches on therapy. That closeted virus comes out with a vengeance when treatment resumes. And the ACTG team found that it can come out in strange ways. They looked closely at genotypic trends in three people with triple-class resistance that reverted to single- or double-class resistance during the treatment hiatus. NNRTI mutations disappeared in all three, and none used an NNRTI in the new regimen. Yet the NNRTI mutations popped back up in all of them. This finding suggests that those mutations shared the same genome with PI or NRTI mutations and rushed back into circulation with renewed treatment.

In 18 people genotyped after the 16-week drug break, six (33 percent) had little or no reversion to wild-type virus, seven (39 percent) had a “partial shift,” and five (28 percent) had an “extensive shift.” But three of those five (60 percent) suffered a virologic failure, and in all three the genotype at failure matched the pre-STI genotype.

The high failure rate among “extensive shifters” comes as no surprise because standard genotyping can’t spot small caches of resistant virus that hangs on during drug breaks. That closeted virus comes out with a vengeance when treatment resumes. And the ACTG team found that it can come out in strange ways. They looked closely at genotypic trends in three people with triple-class resistance that reverted to single- or double-class resistance during the treatment hiatus. NNRTI mutations disappeared in all three, and none used an NNRTI in the new regimen. Yet the NNRTI mutations popped back up in all of them. This finding suggests that those mutations shared the same genome with PI or NRTI mutations and rushed back into circulation with renewed treatment.

Resistance rears up during drug breaks

PART trial researchers reported the emergence or reemergence of resistant virus during STIs tried by people taking their first antiretrovirals [abstract 552]. The ongoing study randomizes people with a viral load below 400 copies/mL to continue therapy for 24 months or to take drug breaks lasting one, one, two, two, and three months broken up by three-month stretches on therapy. Lucia Palmisano (Istituto Superiore di Sanità, Rome) looked for resistance in 136 people in the STI arm, 80 of whom had finished four cycles of intermittent therapy. They had taken their regimen for a median of 27 months and had a median pretreatment CD4 count of 394 cells/mm\(^3\).

So far 39 of the 136 break takers (29 percent) had resistant virus appear at least once during a drug holiday. The most common mutations were M184V in 16 percent taking lamivudine (3TC), L90M in 10 percent taking saquinavir (SQV) or nelfinavir (NFV), and K103N in 8 percent taking an NNRTI. Among 27 of the 39 people who had resistant virus and pre-STI samples, 11 had evidence of resistant virus in baseline HIV DNA. Eliminating those 11, Palmisano counted 11 new mutations after the first drug break, four more after the second, eight more after the third, and one more after the fourth.

Defining virologic failure as a viral load above 400 copies/mL after one or more STIs, the PART team counted 25 failures among 136 in the STI group (18 percent). The failure rate came to 12 percent among people without mutations and 33 percent among those with mutant virus, a significant difference (\(P=0.004\)).

This study confirms earlier reports that resistant virus can evolve during drug holidays.\(^1\)\(^-\)\(^4\) Taking drug breaks while using an NNRTI is particularly hazardous because the long half-lives of these drugs (documented in studies reviewed in the April 2004 IAPAC Monthly\(^5\)\(^-\)\(^6\)) means they linger in the body well after other drugs in the regimen get washed out. Attempts to solve that problem by stopping the NNRTI before stopping the other agents didn’t work in the PART study or one other.\(^2\) Palmisano suggested that prying into proviral DNA to look for mutations may help flag people with a higher risk of failure during drug breaks.

Factors favoring durable suppression and survival

Two studies evaluating people at opposite extremes of the treatment experience spectrum shared a similar conclusion: Treatment breaks — sometimes even brief breaks — raise the risk of virologic failure or death.

Heather Ribaudo (Harvard School of Public Health, Boston) weighed variables that drive virologic failure in people enrolled in ACTG 388, the trial that combined zidovudine (AZT)/3TC with indinavir (IDV), IDV/EFV, or IDV/NFV [abstract 553]. She focused on 517 people with no earlier treatment experience, tracking them for a median of 108 weeks. In that time she counted 172 people with virologic failures, including three whose viral load climbed above the pretreatment level, 32 who had at least a 1-log rise from their lowest viral load, 56 who had more than 200 copies/mL at week 24, and 81 who had a confirmed load above 200 copies/mL after a confirmed load below that mark.

A multivariate analysis identified longer drug breaks as the strongest predictor of failure at the following hazard ratios (HR) and 95 percent confidence intervals (CI):

- 1- to 2-week break: HR 4.24, CI 2.13 to 8.84, \(P<0.0001\)
- More than a 2-week break: HR 9.34, CI 5.95 to 14.71, \(P<0.0001\)
- Off drug: HR 4.20, CI 2.80 to 6.28, \(P<0.0001\)
Even though toxicity explained most treatment interruptions, recent toxicity itself did not correlate with virologic failure. Nor did baseline viral load or intermittent viremia (“blips”) influence failure. Other factors that independently predicted failure were younger age (HR 1.36, CI 1.13 to 1.64, for each 10-year decrement, P = 0.001), being nonwhite or Hispanic (HR 1.47, CI 1.08 to 2.01, P = 0.015), and taking a regimen including IDV/NFV (HR 1.40, CI 0.98 to 2.01, P = 0.06). Compared with AZT/3TC/IDV, AZT/3TC/IDV/EFV lowered the risk of failure (HR 0.58, CI 0.38 to 0.87, P = 0.01).

HIV Outpatient Study (HOPS) investigators, led by Frank Palella (Northwestern University, Chicago), delved for markers of death in 1,252 cohort members who had taken NRTIs, NNRTIs, and PIs for at least six months with each drug class and for a total of at least four years [abstract 555]. The cohort included 624 people who sustained a virologic failure (viral load at or above 10,000 copies/mL or failure to subtract at least a half-log in viral load) with regimens including drugs from all three classes.

For both groups an analysis of deaths per 1,000 person-years stratified by CD4 count and treatment status at last follow-up found that staying on therapy correlated with lower mortality regardless of CD4 count (Table 1). This result confirms earlier studies documenting prolonged survival among people with heavy treatment experience if they keep taking their drugs, even after statistical adjustments to exclude people who probably stopped treatment because they were near death.7,8

In multiple logistic regression analyses, Palella nailed down five other factors that independently predicted longer survival in both heavily pretreated people and those with triple-class failure:

- Starting antiretrovirals at a higher CD4 count
- Having a higher CD4 count when meeting the definition of heavy pretreatment or triple-class failure
- Not having an earlier AIDS diagnosis
- Being younger
- Taking a potent combination as a first regimen

In the heavily experienced group, two other variables favored longer survival:

- Not having a history of injecting drug use
- Taking a greater total number of individual antiretrovirals

**STIs after primary infection**

For some time many assumed that taking STIs after prompt therapy for early infection held the best hope of damping replication enough to allow long times—maybe a lifetime—without antiretrovirals. Those hopes rested on the theory espoused by Bruce Walker (Massachusetts General Hospital, Boston) that speedy treatment would head off demolition of crucial HIV-specific CD4 cells. But three 11th CROI reports dimmed such prospects.

Daniel Kaufmann from Walker’s group tendered the latest update on their closely watched cohort of people first treated before seroconversion [abstract 24]. All 14 pushed their viral loads under 50 copies/mL for several months with early therapy, then stopped antiretrovirals until their RNA reading tarried above 5,000 copies/mL for more than three weeks or peaked above 50,000 copies/mL once.

The virus always bungeed back into detectable territory during the drug holidays, despite surging HIV-specific CD8-cell responses during the first drug break. Still, 11 of the 14 (79 percent) managed to keep the medicine cabinet closed for 90 days or longer. And by intention-to-treat analysis, eight (57 percent) went without antiretrovirals for at least 180 days, six (43 percent) for at least 360 days, and three (21 percent) for at least 720 days. But most people saw their viral load inch up and their CD4 cells drop during the days without drug—signals that their immune system alone had not handcuffed HIV. As Kaufmann observed, the noncomparative design of this study makes it impossible to say whether STIs offer any virologic benefit after control of primary infection.

The French PRIMSTOP study found that only one of 26 people (4 percent) who took structured breaks after treatment for primary infection met the primary endpoint—a viral load below 50 copies/mL over a 24-week drug break following three shorter breaks [abstract 395]. All 26 stayed off treatment for at least six months, although three added PI-resistant virus to their charts during the trial.

Bruno Hoen (University Hospital, Besançon, France) enrolled 29 people with symptomatic primary HIV infection who had not fully seroconverted, but three dropped out of the study. Everyone took the same regimen—

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**Table 1. Mortality among people on versus off therapy with heavy treatment experience**

<table>
<thead>
<tr>
<th>CD4 stratum (cells/mm³)</th>
<th>On therapy</th>
<th>Off therapy</th>
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<tbody>
<tr>
<td>0 to 50</td>
<td>63</td>
<td>179</td>
</tr>
<tr>
<td>51 to 200</td>
<td>12</td>
<td>89</td>
</tr>
<tr>
<td>201 to 350</td>
<td>5</td>
<td>34</td>
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<tr>
<td>351+</td>
<td>3</td>
<td>20</td>
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**Deaths per 1,000 person-years among people with heavy treatment experience***

<table>
<thead>
<tr>
<th>CD4 stratum (cells/mm³)</th>
<th>On therapy</th>
<th>Off therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 50</td>
<td>84</td>
<td>179</td>
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<tr>
<td>51 to 200</td>
<td>30</td>
<td>117</td>
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<tr>
<td>201 to 350</td>
<td>4</td>
<td>62</td>
</tr>
<tr>
<td>351+</td>
<td>7</td>
<td>16</td>
</tr>
</tbody>
</table>

*See text for definition.

Source: Frank Palella, abstract 555.
didanosine (ddI), stavudine (d4T), hydroxyurea, and NFV—for 34 weeks and got their viral load below 50 copies/mL. Then they took drug breaks lasting two, four, and eight weeks followed by 12 weeks back on treatment. At week 84 everyone stopped their antiretrovirals, and follow-up continued to week 108.

The protocol was no picnic. Seven people landed in the hospital, including two with acute fever and four with “nervous depression” or “malaise.” Four people had laps in lipase (without clinical pancreatitis), two had peripheral neuropathy, one had ureteric colic, and one atrial flutter. Fifteen of the original 29 (52 percent) abandoned hydroxyurea.

Only one variable—being a woman—correlated with a viral load below 1,000 copies/mL at week 108 in a univariate analysis. Factors that did not influence this outcome were age; baseline CD4 count, HIV RNA, or HIV DNA; Western blot status at baseline (less than four versus four or more bands); HIV DNA at week 84; or sticking with hydroxyurea throughout the study.

In an on-treatment analysis, five of 26 people (19 percent) kept their viral load below 1,000 copies/mL from week 84 to week 108, and seven (27 percent) had a sub-1,000 reading at week 108. As in the Massachusetts General study, standard measures of immune response did not favor better viral control. Neither baseline nor week-84 CD4- or CD8-cell interferon-gamma response or CD4-cell proliferative response singled out people with better viral control.

PRIMSTOP adds to the small but ever-growing roll of resistant virus emerging during drug breaks. Three people without the NFV-linked L90M mutation before treatment had it after week 84. (Virus resistant to 3TC cropped up without the NFV-linked L90M mutation before treatment resistant virus emerging during drug breaks. Three people had leaps in lipase (without clinical pancreatitis), two had peripheral neuropathy, one had ureteric colic, and one atrial flutter. Fifteen of the original 29 (52 percent) abandoned hydroxyurea.

Desquilbet noted that the apparent lack of any virologic benefit for treatment followed by an interruption “must be confirmed in a randomized trial involving an untreated control group and long-term post-trial follow-up.” All told, though, these three studies clearly fail to erect a rationale for quick treatment of early infection followed by supervised drug breaks. The emergence of resistance and the danger of serious side effects (at least with regimens like the PRIMSTOP combo) argue that the tactic poses more risks than it promises benefits.

Does quick therapy during primary infection offer other advantages, such as blocking virus from the resting CD4-cell reservoir? Not among infants treated within 0.6 to 4.8 months of birth, reported Deborah Persaud (Johns Hopkins University, Baltimore) [abstract 387]. Although the children continued successful therapy for a median of four years—and seven of them (60 percent) never seroconverted—they had as much replication-competent HIV in resting infected cells as children who never started therapy until they reached the chronic infection stage. The mean number of latently infected cells measured 0.92 per million cells in the early treatment group and 1.4 per million cells in children first treated in chronic infection, a nonsignificant difference (P = 0.55).

Persaud believes the findings “support the notion that the resting CD4 T-cell latent reservoir is fully established and reaches equilibrium during acute HIV-1 infection in children.”

**Are there ways to make STIs work better?**

Although STIs may not point the way to the promised land—an immune system that controls HIV consistently without drugs—several studies now show that many people who started antiretrovirals early in their disease course or responded well can put treatment on hold for a year or more without disease progression or dangerous T-cell drops. So researchers have started looking for ways to stretch the time people with well-controlled replication can safely go without antiretrovirals.

Keith Henry (University of Minnesota, Minneapolis) and ACTG A5102 colleagues tried three rounds of interleukin-2 (IL-2) in people with a CD4 count above 500 cells/mm³ and a viral load below 200 copies/mL [abstract 510]. The ACTG team randomized 23 people to take three...
five-day cycles of IL-2 subcutaneously at a dose of 4.5 million units twice daily every eight weeks while continuing their antiretrovirals and 24 people to continue their antiretrovirals without IL-2. At the end of this span everyone with a CD4 count over 500 cells/mm$^3$ shelved their antiretrovirals until the count fell to 350 cells/mm$^3$. No study participant ever had an earlier virologic failure on a potent regimen, and the median nadir CD4 count measured 344 cells/mm$^3$.

The median CD4 count rose from 790 to 1,331 cells/mm$^3$ during IL-2 therapy but did not change in the control group. Ten people had grade 3 or 4 clinical symptoms while taking IL-2, four had grade 3 or 4 lab toxicities, and seven had grade 3 or 4 side effects, compared with zero, three, and three in the control arm. But no one fled the study because of these flares. Two people appeared to have the acute retroviral syndrome when taking a drug break.

The median CD4 count in the IL-2 group measured 661 and 671 cells/mm$^3$ at weeks 24 and 48 of the STI, compared with 540 and 485.5 cells/mm$^3$ in the control group. Two people in the IL-2 group and six in the control group had to restart therapy, and the time to restarting proved significantly longer in the IL-2 group ($P = 0.039$). Follow-up will continue in this trial.

A nonrandomized study used another immune modulator, mycophenolate mofetil (MMF), to try to prolong time off therapy in 14 people who started antiretrovirals during primary infection [abstract 400]. The strategy rests on MMF’s ability to shrink the pool of dividing and activated CD4 cells. Giuseppe Rizzardi (San Raffaele Hospital, Milan) gave 500 mg of MMF twice daily two weeks before suspending antiretrovirals in the 14 volunteers, who had maintained an undetectable viral load for an average 3.6 years on therapy. The plan called for continuing MMF alone until the viral load rose above 100,000 copies/mL. The comparison group included six people who stopped treatment without MMF. These people had maintained an undetectable viral load for an average 2.3 years.

After 58 weeks of follow-up, three of 14 in the MF group and four of six in the control group had to restart therapy. The 11 taking MMF who stayed off therapy kept their viral load below 20,000 copies/mL most of the time and had a stable or dwindling cache of HIV DNA. Their mean CD4 count ($\pm$ standard deviation) fell from 1,020 ($\pm$ 266) cells/mm$^3$ when they stopped their antiretrovirals to 795 ($\pm$ 61) cells/mm$^3$ at week 58. The viral load rebound slope in the MMF group rose significantly more slowly than in the control group ($P = 0.03$). No one suffered major side effects from MMF.

Although not too much can be made of the case-control comparison in this study, the results do hint that MMF helps keep HIV under wraps. Of the 11 people who stayed off therapy, five had occasional viral load readings between 20,000 and 100,000 copies/mL, but four of those five had only one such reading through 78 weeks of follow-up.

Another group at Milan’s San Raffaele Hospital tried a more taxing tactic to improve responses after an STI in people with triple-class-resistant virus [abstract 664]. They purged their monocytes with six apheresis sessions during a presalvage STI. Hamid Hasson randomized six people to have apheresis and six to take their drug break without ousting monocytes. Although everyone had at least a six-year treatment history and most had tried nine or 10 antiretrovirals, they started the study with decent CD4 counts, averaging 685 ($\pm$ 241.5) cells/mm$^3$ in the apheresis group and 495 ($\pm$ 145.7) cells/mm$^3$ in the control group. Viral loads average 4.05 logs in the apheresis arm and 4.18 logs among controls.

Viral loads did not differ significantly between treatment groups during the drug break. But the people who shed monocytes maintained better viral control after therapy resumed. Five of six people in the apheresis group, versus two of six controls, reached a viral load below 400 copies/mL and kept it there through an average 66.5 weeks of follow-up. The apheresis group also enjoyed a bigger CD4 bounce when they restarted therapy, averaging a 483.5-cell/mm$^3$ gain versus 166.5 cells/mm$^3$ among controls ($P = 0.033$).

What explains these differences? Hasson and colleagues aren’t sure. They tried depleting monocytes because of studies showing that: (1) infectious HIV sits in monocytes of people on prolonged antiretroviral therapy, (2) antiretroviral-induced viral decay is slower in monocytes than in resting or activated CD4 cells, and (3) in their own work, apheresis is safe, leads to stable CD4 gains, cuts the number of circulating cells carrying HIV DNA, and lowers monocyte production of the cytokine tumor necrosis factor alpha in people not responding to potent antiretrovirals. They speculated that purging monocytes may promote release of drug-sensitive HIV from cellular reservoirs. But they didn’t report drug susceptibilities before the STIs or after therapy resumed. After the STI most people in both groups switched to lopinavir/ritonavir (LPV/RTV), often with an NNRTI or amprenavir (APV).
Guided treatment breaks in children

If studies of suspended therapy make sense in adults with tightly controlled HIV infection, they make even more sense in children who might otherwise face a life sentence of antiretroviral toxicity. Two 11th CROI studies showed that well-planned drug breaks can be safe—and lengthy—in children with diverse treatment histories.

Claudia Fortuny (Hospital Sant Joan de Déu, Barcelona) reported drug holiday results in three groups of children—three toddlers with drug-susceptible virus taking the same regimen they started before an age of eight weeks; seven children with drug-susceptible virus who were first treated after the age of two years; and 10 children with multidrug-resistant virus who had taken several regimens [abstract 947]. These clinicians considered treatment interruptions to address toxicity, poor response, or parents’ wishes. All children had to be asymptomatic with a CD4 percent above 25 percent, and all agreed to resume therapy if the acute retroviral syndrome developed (it never did), if they suffered disease progression (they didn’t), or if the CD4 tally fell below 17 percent or 350 cells/mm3.

After a median 17 months of follow-up (range five to 41 months), all children remained clinically stable and three restarted their antiretrovirals. Two resumed treatment because their CD4 percent sank to 14 percent, and one because of her parents’ decision. Both children who resumed treatment because of low CD4 percents regained CD4 cells and controlled viral replication. Among the other 17 children, only three had a CD4 drop below 25 percent, and all three maintained a total CD4 count above 350 cells/mm3. The median viral load climbed from 3.8 logs (range 2.9 to 5.4 logs) when the treatment break began to 4.4 logs (range 3.9 to 5.7 logs) at last follow-up (P = 0.02). The nine children who stopped therapy because of antiretroviral toxicity all enjoyed improvements in these conditions (lipodystrophy, anemia and failure to thrive, hepatotoxicity with HCV coinfection, anorexia, diarrhea, and vomiting).

Ram Yoigel (Chicago Children’s Memorial Hospital) and coworkers at six other US sites studied progressively lengthening treatment breaks in 12 children and young adults (more than four to 21 years old) who had maintained a viral load under 400 copies/mL for the past year and had fewer than 50 copies/mL at screening [abstract 948]. All were taking a PI-based regimen that did not include an NNRTI or abacavir (ABC). The STI schedule pushed up the time off treatment by two days with each break:

- Three-day STI
- Three weeks back on therapy
- Five-day STI
- Three weeks back on therapy

And so on until the viral load peaked above 50 copies/mL during a drug break. When that happened the study participant took antiretrovirals until the viral load slipped under 50 copies/mL then resumed the two-day STI escalation schedule.

HIV broke through the 50-copy barrier as early as five days in some and as late at 11 days in others. Everyone managed to regain a sub-50 load with renewed therapy. In seven people who have reached the 19-day STI cycle, median CD4 changes from baseline measured -1 percent (range -10 to +5 percent) and -165 cells/mm3 (range -839 to +698 cells/mm3). Viral loads rebounded higher with each successive STI until the breaks reached 15 to 19 days, when the rebounds leveled off. Consensus sequencing detected no new resistance mutations.

OLD DRUGS TO THE RESCUE

Besides the two reports on presalvage drug breaks (abstracts 58 and 664 above), the 11th CROI served up plenty of other news on salvage and rescue regimens. The more compelling of these reports featured new ploys with old drugs rather than breakthroughs with brand new agents. In the new drug category, attendees heard reports on TMC114 in multi-PI-experienced people, TMC125 in NNRTI-resistant mutants, and d-d4FC (reverset), a nucleoside active against NRTI-resistant virus, in treatment-naive volunteers. But more immediately useful findings came from studies of ritonavir-boosted PIs—sometimes at very high or very low doses.

Can you boost LPV levels?

Standard-dose LPV/RTV can handle some PI-resistant virus. But can a higher dose handle more? That’s the question Richard Bertz (Abbott Laboratories) set out to answer in an open-label study of 36 people with multiple PI and NNRTI experience randomized to one of two doses of LPV/RTV:

- 667/167 mg (five 133/33-mg capsules) twice daily with food
- 400/100 mg (three 133/33-mg capsules) twice daily with food

Everyone also took two or three NRTIs picked by the clinician. Bertz and colleagues measured LPV levels over 12 hours at week three and used those numbers to figure lopinavir’s inhibitory quotient (IQ), the trough level divided by lopinavir’s 50 percent inhibitory concentration. People began high-dose LPV/RTV with a median CD4 count of 91 cells/mm3 (range 2 to 679 cells/mm3), a median
viral load of 4.7 logs (range 3.1 to 5.9 logs), and a median of five LPV-linked mutations (range zero to eight).

Bertz found no differences between the doses in virologic response at 48 weeks. The time-averaged difference from baseline viral load measured -1.39 logs (range -3.47 to +0.41) for all study participants. Twenty-one people (58 percent) reached a viral load below 400 copies/mL. The 667/167-mg dose seemed to be more tolerable.

In a multivariate analysis two factors independently predicted viral load change from baseline—number of (genotypically determined) active NRTIs in the new regimen (\(P = 0.04\)) and a higher LPV IQ (\(P = 0.007\)). A similar analysis of factors favoring a 48-week viral load below 400 copies/mL found three: higher LPV IQ (\(P = 0.03\)), lower baseline viral load (\(P = 0.03\)), and number of active NRTIs (\(P = 0.05\)).

Bertz concluded that “higher doses of LPV/RTV may provide LPV concentrations sufficient to overcome certain degrees of reduced LPV phenotypic susceptibility, resulting in a significant treatment effect.” Higher LPV levels did not correlate with higher lipid elevations in a recent careful study of 55 people taking 400/100 or 533/133 mg of LPV/RTV twice daily.17 But triglycerides rose an average 8.5 mg/dL of 55 people taking 400/100 or 533/133 mg of LPV/RTV. Higher LPV levels did not provide LPV concentrations sufficient to overcome certain degrees of reduced LPV phenotypic susceptibility, resulting in a significant treatment effect.” Higher LPV levels did not correlate with higher lipid elevations in a recent careful study of 55 people taking 400/100 or 533/133 mg of LPV/RTV twice daily.17 But triglycerides rose an average 8.5 mg/dL of 55 people taking 400/100 or 533/133 mg of LPV/RTV.

**LPV/RTV vs ATV/RTV or ATV/SQV**

If high lipids cause high anxiety with LPV/RTV, should clinicians turn to lipid-friendly once-daily atazanavir (ATV) plus a second PI? An international, open-label, randomized trial funded by Bristol-Myers Squibb and reported by Edwin DeJesus (IDC Research Initiative, Altamonte Springs, Florida) rated once-daily ATV/RTV (300/100 mg) noninferior to twice-daily LPV/RTV (400/100 mg) in people who had tried an average of 2.5 PIs and 1.4 NNRTIs plus five or so NRTIs [abstract 547]. But once-daily ATV/SQV (400/1,200 mg) did not do as well as either of the other regimens.

The trial randomized 358 people to one of the three PI regimens for two weeks with current NRTIs. Study groups didn’t differ in the number of primary NRTI, NNRTI, or PI mutations when switching to their new regimen (\(P = 0.05\)).

Study participants started a new regimen of three retrovirals appear to work better when faced with M184V virus replicates poorly and that some other anti-retrovirals appear to work better when faced with M184V. Those traits did nothing to help the 65 people randomized to continue 3TC in this trial.

Study participants started a new regimen of three or more drugs, picked by their treating physician, with or without continued 3TC. Fifty-five people were taking their first failing regimen, and 76 their second or later failing combination. They averaged 310 cells/mm\(^3\) and a viral load around 1,000 copies/mL. Study groups didn’t differ in the number of primary NRTI, NNRTI, or PI mutations when switching to their new regimen.

Yet substantially more people quit the APV/RTV group before week 48 (21 percent) than gave up on LPV/RTV (10 percent). The lion’s share of those dropouts resulted from “treatment failure/lack of efficacy”: 14 percent with APV/RTV versus 5 percent with LPV/RTV. Rates of total treatment-related side effects proved similar with these two regimens (29 percent with APV/RTV and 25 percent with LPV/RTV), as did “serious adverse events” (10 percent with APV/RTV and 9 percent with LPV/RTV). And, yes, lipid changes over 48 weeks strongly favored APV/RTV over LPV/RTV (Table 2).

**Continue or stop 3TC?**

One gritty bit of controversy has stayed stuck in the gullet of HIV research for many a year: whether to continue 3TC when a regimen fails or whether to retire the drug. An 18-site study involving 133 people may finally clear this pesky irritant [abstract 549]. Keeping 3TC did no good in this population, reported Ulrich Dragsted (Copenhagen HIV Program) and colleagues, although the study started too soon for people with 3TC-resistant virus to profit from TDF.

The argument to stick with 3TC even after it evokes its signature M184V mutation rests on findings that M184V virus replicates poorly and that some other anti-retrovirals appear to work better when faced with M184V. Those traits did nothing to help the 65 people randomized to continue 3TC in this trial.

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**Table 2. Lipid changes after 48 weeks of ATV/RTV versus LPV/RTV**

<table>
<thead>
<tr>
<th></th>
<th>ATV/RTV (300/100 mg qd)</th>
<th>LPV/RTV (400/100 mg bid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>-8*</td>
<td>+6</td>
</tr>
<tr>
<td>Fasting LDL-C</td>
<td>-10</td>
<td>+1</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-7</td>
<td>+2</td>
</tr>
<tr>
<td>TG</td>
<td>-4*</td>
<td>+30</td>
</tr>
</tbody>
</table>

*\(P \leq 0.005\) versus LPV/RTV.

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

Source: Edwin DeJesus, abstract 547.
About half of the people in both treatment arms regained control of viremia and sawed 1.4 logs off their viral load. As expected, people who continued 3TC maintained the M184V mutation, while those who stopped 3TC did not. One may speculate that results could have differed if more participants had taken TDF, because M184V enhances susceptibility to TDF. Only one person in the trial took TDF, and that person was in the group that stopped 3TC.

**Pressure tactics: A new salvage stratagem?**

Grading the current gaggle of salvage strategies, Odile Launay (Cochin Hospital, Paris) and colleagues at other Paris units didn’t like what they saw [abstract 649]:

- Presalvage treatment interruptions may call forth more drug-susceptible virus, which multiplies more nimbly than resistant virus.
- Cutting back to a single drug class may also favor partial reversion of resistant virus to wild-type.
- Maintaining a full-dose regimen heightens threats of toxicity and further resistance.

So they hypothesized that “a calibrated reduction in drug pressure exerted both on protease and reverse transcriptase could stabilize the evolution and pathogenic potential of resistant virus.” Here’s how they put that theory to the test:

Launay and colleagues recruited 26 people in whom more than one PI regimen failed and with fewer than two active drugs available according to the ANRS resistance algorithm. They put everyone on a regimen of twice-daily IDV/RTV (200/100 mg) plus standard twice-daily 3TC. At week two they measured IDV levels and, if necessary, bumped the dose to 400/100 mg twice daily to aim for a trough of 150 to 350 ng/mL. People began the low-pressure regimen with a median eight-year treatment history, a median CD4 count of 340 cells/mm³, and a median viral load of 4.48 logs.

After 24 weeks of follow-up, one could argue for certain advantages to the reduced-dose gambit, but it’s not about to become this year’s salvage standard of care. On the plus side, the number of resistance mutations didn’t change much, as one would expect with lowered drug pressure. The 3TC-associated M184V did debut in three people. At the same time the low-dose combo did nothing to slow progression. Viral loads continued to rise at a significant pace (median 0.22 log, \( P = 0.003 \)) and CD4 counts dipped by a median of 49 cells/mm³ (\( P < 0.001 \)). Launay argued, though, that this drop did not significantly exceed the slide seen in the preceding six months, when people were still taking their full-dose regimen.

Because the trial was not randomized, there’s no way to figure whether the low-pressure strategy heightened the risk of clinical progression.

No one had a new AIDS diagnosis during the 24 weeks, but 10 people (38 percent) reached a primary endpoint—six who lost 25 percent or more of their CD4s, three whose viral load climbed at least 0.7 log, and one who met both failure criteria. Serious toxicities included one case of hyperbilirubinemia, one myocardial infarction, and one case of thrombocytopenia with hepatitis.

**Resistance busters: The TMCs and reverset**

Two protease inhibitors that may help people with PI-resistant virus perch on the treatment horizon—tipranavir and TMC114. Two reports on the later agent, a Tibotec product, appeared at this meeting.

Monika Peeters and Tibotec colleagues randomized 50 people with plentiful PI experience to continue their current PI regimen for eight weeks or to switch the PI to one of three TMC114/RTV doses—300/100 or 600/100 mg twice daily, or 900/100 mg once daily [abstract 533; see note 18]. Everyone had taken two to four PIs (not counting low-dose RTV), and everyone continued their current NRTI. People taking a floundering NNRTI regimen could not enroll in the trial.

Twenty-six people (52 percent) had virus resistant to all PIs licensed at the time of the trial (which excluded ATV), and 11 (22 percent) had virus sensitive to two or more PIs. At baseline the median fold change in susceptibility to TMC114 compared with wild-type virus measured 1.70 (range 0.3 to 26.6), the fold change in susceptibility to LPV ranged from 24.7 to 97.20, and the fold change in susceptibility to all PIs (excluding TMC114) ranged from 5.3 to 92.40. The median baseline viral load stood at 4.26 logs (about 18,000 copies/mL) and the median CD4 count at 305 cells/mm³.

After eight weeks of treatment the median time-averaged difference in viral load and absolute drop in viral load among people switching to TMC114/RTV significantly exceeded viral load changes in people staying with the same PI (Table 3). Several baseline variables analyzed had no significant impact on the 14-day virologic response to TMC114/RTV:
Another Tibotec team led by Sandra De Meyer analyzed the susceptibility of 5,601 clinical isolates to TMC114 and to all licensed PIs [abstract 620; see note 18]. Among those isolates, 2,202 had more than a 4-fold change in 50 percent effective concentration compared with wild-type virus for at least one PI. Of those 2,202, 97 percent had more than a 4-fold change in susceptibility to NFV, 81 percent to RTV, 68 percent to LPV, 64 percent to IDV, 62 percent to ATV, 51 percent to SQV, 47 percent to APV, and 20 percent to TMC114.

Among isolates with more than a 4-fold change in susceptibility to all seven approved PIs, 52 percent remained susceptible to TMC114 at the 4-fold cutoff, and 79 percent of those resistant to six approved PIs remained susceptible to TMC114. De Meyer grouped 739 isolates that had been genotyped into clusters with one, two, three, or more primary PI mutations. The median fold change in susceptibility to TMC114 remained at or below 4-fold for each of these subgroups.

Another Tibotec agent—the NNRTI TMC125—also stirred interest in the resistance poster aisles. Attendees at the 9th CROI learned that seven days of TMC125 as a substitute for failing EFV or NVP lowered viral loads by a median 0.89 log in 14 people.19 At this year’s meeting attendees got a look at resistance to TMC125 in single, double, and triple mutants constructed by site-directed mutagenesis [abstract 621; see note 18].

Tibotec’s Johan Vingerhoets reported that only four of 51 single-mutant strains had more than a 10-fold change in susceptibility to TMC125: Y181I, Y181V, F227C, and M230L. Those mutants made up 1.4, 0.97, 0.01, and 0.98 percent of 7,144 isolates sent to Virco and proving resistant to at least one of the current NNRTIs. Of 19 double mutants constructed, one (V179F + Y181C) had more than 10-fold resistance to TMC125. This double mutant represented 0.53 percent of the 7,144-isolate database. Among more prevalent double mutants containing the changes L100I, K103N, Y181C, and G190A, none had more than a 10-fold change in susceptibility to the Tibotec drug.

Vingerhoets concocted one triple mutant, K103N + Y181C + G190A, because it shows up in 5.7 percent of the NNRTI resistance database. This mutant’s fold change in susceptibility to TMC114 measured 1.7 (versus a 44-fold change in susceptibility to EFV). Four other triple mutants built because TMC125 selected component mutations in in vitro experiments had more than 10-fold resistance to the NNRTI. They included L100I + K103N with either Y181C or T386A and K103N + Y181C with either V179I or Y318F.

For people who need another nucleoside that can handle NRTI-resistant virus, reverse (d-d4FC) gained notice at this year’s conference thanks to some PowerPoint persuasion by Robert Murphy (Northwestern University, Chicago) [abstract 137]. This NRTI is a cytidine analog, like 3TC and emtricitabine (FTC). With a torpid intracellular half-life of 17 hours, it could join ddi, d4T, 3TC, TDF, and FTC as once-daily options.

This pilot trial randomized 30 treatment-naive people to take 50, 100, or 200 mg of d-d4FC or placebo once daily for 10 days. On day 11 the average viral load had dropped 1.67 logs with 50 mg, 1.74 logs with 100 mg, and 1.77 logs with 200 mg. Murphy noted that in vitro results of earlier work suggest the 200-mg dose would be active against all NRTI-resistant mutants except the multinucleoside-resistant D69S insertions and Q151M complex. The maximum concentration achieved with 200 mg exceeds the 90 percent inhibitory concentration of the K65R mutation, M184V, and multiple thymidine analog mutations. But d-d4FC does select the K65R mutation in vitro, as do ddi, d4T, 3TC, TDF, and FTC as once-daily options.

Nearly half of the study participants complained of cold symptoms, 33 percent had headaches, and 17 percent fatigue. But side effects rates among people taking d-d4FC didn’t differ from those taking placebo, and no one dropped out of the study because of side effects. A phase 2 trial will size up d-d4FC in people with NRTI-resistant virus.

Two resistance busters that had their day in the spotlight of meetings past did not return for curtain calls at this year’s conclave. T-1249, the second-generation fusion inhibitor active against virus resistant to ENF, and amdoxovir (DAPD), a nucleoside that stymies some NRTI-resistant virus, both earned early retirement in the weeks before the meeting. Roche and Trimeris figured that making big batches of T-1249 would not return the investment, and Gilead dropped DAPD to focus on less toxic candidates.

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**Table 3. Viral load changes after eight weeks of TMC114/RTV versus continued failing PI**

<table>
<thead>
<tr>
<th>Treatments</th>
<th>n</th>
<th>Median DAVG</th>
<th>Median RNA drop</th>
<th>P vs control</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMC114/RTV 300/100 mg bid</td>
<td>13</td>
<td>-0.56</td>
<td>1.24 logs</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TMC114/RTV 600/100 mg bid</td>
<td>12</td>
<td>-0.81</td>
<td>1.50 logs</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TMC114/RTV 900/100 mg qd</td>
<td>10</td>
<td>-0.70</td>
<td>1.25 logs</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Failing PI</td>
<td>11</td>
<td>-0.03</td>
<td>-0.02 log</td>
<td></td>
</tr>
</tbody>
</table>

*Everyone continued the same NRTIs for 8 weeks.

bid = twice daily; DAVG = time-averaged difference in viral load; qd = once daily.

Source: Monika Peeters, abstract 533.
These retreats offered timely reminders that pitfalls abound on the road to developing resistance-resistant drugs.

This CROI was rich in reports on the motley interplay of HIV, antiretrovirals, obesity, glucose, lipids, and — inevitably — diabetes and heart disease. And much of the news brought little cheer. The prevalence and incidence of hyperglycemia and diabetes are higher in gay men taking antiretrovirals than in gays without HIV infection. Obesity is epidemic in a Pennsylvania cohort of people with HIV, especially black women. A fresh update from the Kaiser Permanente clinics in northern California charts a doubling of hospital admissions for heart disease in HIV-infected people compared with uninfected controls. Combining pravastatin with fenofibrate didn’t help many people reach standard lipid goals. In another study, fish oil didn’t help much either.

Any rays of hope? ATV appears to upset glucose as little as it does lipids. The massive multicohort DAD study failed to link high blood pressure to antiretroviral therapy (though a smaller study of US women reached the opposite conclusion). And, for HIV-infected people who already have clogged coronary arteries, stitching in new vessels looks “feasible and safe.”

Glucose, insulin, obesity, diabetes

In a substudy of ACTG 384, Michael Dubé (Indiana University, Indianapolis) found no difference in insulin resistance when comparing people treated with NFV or EFV [abstract 74]. The analysis involved 99 people randomized to NFV and 110 to EFV (both with AZT/3TC or ddI/d4T). The groups were comparable in baseline glucose and insulin measures and in percent with a family history of diabetes (37 percent with EFV and 30 percent with NFV).

HOMA-measured insulin resistance rose little in either group during the first weeks of treatment, a finding Dubé took to mean that insulin resistance is not a PI class effect. In an intent-to-treat analysis, insulin resistance worsened by 10 percent by treatment week 48 (P < 0.05) with no difference between the EFV and NFV arms or the AZT/3TC and ddI/d4T arms. Dubé noted that the intent-to-treat analysis makes it impossible to rule out the chance that switching regimens during the study — which was part of the trial design — affected the results. The ACTG will run an on-treatment analysis to see if that happened.

A randomized, double-blind, placebo-controlled crossover study in healthy men confirmed clinical findings that ATV has relatively little impact on insulin resistance or triglycerides while LPV/RTV boosts both [abstract 702]. Mustafa Noor (Bristol-Myers Squibb) studied 14 white, nine African-American, and seven Hispanic men who checked into the company’s clinical pharmacology unit for six days of treatment with ATV (400 mg daily), LPV/RTV (400/100 mg twice daily), or ATV placebo.

After six days Noor measured insulin-mediated glucose disposal with the gold-standard glucose clamp method after first gauging triglyceride changes. Two weeks later, everyone returned for another six days and got randomly assigned to a regimen they didn’t receive in the first six days.

Insulin-stimulated glucose disposal and glycogen storage rates proved significantly lower with LPV/RTV than with either ATV or placebo, while triglycerides rose significantly higher in the LPV/RTV arms than in the ATV or placebo arms (Table 4). Atazanavir did not differ from placebo by any of these measures.

Noor observed that an earlier study that he coauthored found little impact of LPV/RTV on glucose disposal after four weeks. But that study gauged insulin resistance by glucose tolerance testing, not the clamp method. And the earlier study did record jumps in free fatty acids and triglycerides, both markers of insulin resistance.

“Although we have studied acute effects [of PIs] in healthy men,” Noor concluded, “long-term results from clinical trials indicate that the extent and severity of metabolic complications are compounded by HIV and occur regardless of gender.”

As these studies confirm, certain antiretrovirals unringe glucose metabolism and so raise the risk of diabetes. A rueful irony here will escape few readers: Before potent therapies came along, HIV infection was largely a wasting disease. Now that people live longer with antiretrovirals, the threats of overweight and obesity — and diabetes — loom. To be sure, generalized wasting, defined as a body mass index (BMI) below 20 kg/m², has not vanished in antiretroviral-treated cohorts. Valerianna Amorosa (University of Pennsylvania, Philadelphia) found wasting in about 10 percent of 1,654 people with HIV [abstract 879]. But overweight and obesity proved nearly five times more prevalent.

This cohort was 78 percent male and 60 percent black. Half were taking potent antiretroviral therapy, 27 percent with a PI. Defining overweight as a BMI from 25 to 29.9 kg/m² and obesity as a BMI of 30 kg/m² or more,
Amorosa chalked up a 46 percent overall prevalence of overweight plus obesity, a 58.8 percent prevalence in women versus 42.4 percent in men, and a 62.1 percent rate in African American women. The prevalence of obesity alone measured 28.5 percent in women and 10.6 percent in men.

In a multivariate model including gender, race, age, smoking, history of injecting drug use, CD4 count, viral load, antiretroviral regimen, income, education, and employment, three factors—female gender, black race, and a higher CD4 count—raised the risk of overweight and obesity while smoking lowered the risk (at the following odds ratios and 95 percent CIs):

- Female versus male: OR 1.99 (1.5 to 2.64)
- Black versus nonblack: OR 1.29 (1.01 to 1.63)
- CD4 count per 100-cell increment: OR 1.12 (1.08 to 1.17)
- Current smoker: OR 0.61 (0.49 to 0.77)

Although these statistics inspire concern over the morbid consequences of overweight in people already facing viral and antiretroviral risk factors for diabetes and heart disease, Amorosa’s HIV cohort looked a good deal slimmer than the Philadelphia population at large. Black men and women and nonblack men in Philadelphia all have significantly higher rates of overweight and obesity than the HIV cohort ($P < 0.001$ for all comparisons), while rates in nonblack women did not differ between the cohort and the population at large.

Amorosa did not report rates of high glucose or diabetes in these Philadelphians with HIV, but Todd Brown (Johns Hopkins University, Baltimore) figured their prevalence and incidence in gay men enrolled in the Multicenter AIDS Cohort Study [abstract 73]. His numbers showed that antiretroviral therapy raises the risk of both prevalent (baseline) and incident (newly diagnosed) diabetes in men taking potent antiretrovirals compared with HIV-seronegative men.

The study group included 1,278 men who entered the cohort from 1999 to 2002. At their first visit, 710 did not have HIV infection, 568 did, and 438 of those 568 were taking potent antiretrovirals. Defining diabetes as a fasting blood glucose of at or above 126 mg/dL, use of antidiabetic drugs, or self-reported diabetes, Brown calculated that antiretroviral-treated men had a 5.3 times higher risk of diabetes than the uninfected group in an analysis adjusted for age and BMI.

To reckon the rate of newly diagnosed high glucose or diabetes, Brown eliminated cohort members with a fasting glucose above 105 mg/dL, use of antidiabetics, or self-reported diabetes. Of the 765 men left, 407 did not have HIV, 358 did, and 272 were taking antiretrovirals. The incidence of hyperglycemia came to 9.1 per 100 person-years in the antiretroviral-treated group versus 5.7 per 100 person-years in the uninfected group. Adjusting for age and BMI at study entry, Brown determined that antiretroviral therapy raised the risk of hyperglycemia 2.16 times. The rate of newly diagnosed diabetes came to 4.9 per 100 person-years in the antiretroviral group and 1.5 per 100 person-years in the uninfected group, to yield a 4.37 times higher adjusted risk in the men taking antiretrovirals.

Among antiretroviral-treated men, any PI, d4T, and EFV all upped the risk of incident hyperglycemia or diabetes. But Brown could nail down no differences between particular drug regimens. The risk of newly diagnosed hyperglycemia also proved higher in men with a pretreatment CD4 count at or below 100 cells/mm$^3$ versus above 300 cells/mm$^3$. But the number of men in this analysis was too small to allow a firm conclusion about the impact of baseline CD4 count. Early analyses suggest that hepatitis C virus coinfection may also raise the risk of high glucose or diabetes in this cohort.

**ART, HDL, CHD, BP, and CRP**

Dubé’s already noted analysis of risk markers in people taking NFV or EFV in ACTG 384 tracked significant jumps in total cholesterol, high-density lipoprotein cholesterol (HDL-c), non-HDL-c, and triglycerides in the group as a whole through treatment week 64 ($P < 0.0001$ for all gains) [abstract 74]. The proportion of lipid substudy participants with total cholesterol above 200 mg/dL rose from 5 percent before treatment to 10 percent at week 64. Proportions with non-HDL-c and triglycerides above 160 mg/dL climbed from 16 percent for both measures at baseline to 48 percent for both at week 64. HDL-c rose significantly more with EFV than with NFV ($P < 0.05$). As a result, the total-to-HDL-c ratio improved more with EFV. But treatment arms did not differ significantly in non-HDL-c or triglyceride hikes.

How do trends like these translate into coronary care unit beds filled by people with HIV? Two large cohort studies published in the months before the meeting came up with the same unhappy answer: The longer you take potent antiretrovirals, the bigger the risk becomes. The multicohort DAD study logged a 26 percent higher myocardial infarction (MI) incidence for every extra year of antiretrovirals. And the French Hospital Database on HIV recorded a growing MI risk among men taking PIs longer than 18 months compared with the general French male population.
heart disease (CHD) and MI when comparing HIV-infected men and men without HIV.23 Klein’s latest update on this cohort did indict PIs as an independent risk for CHD or MI, but so far longer PI use has not significantly raised rates of CHD or MI [abstract 739].

Klein’s analysis involved 4,762 men with HIV (21,951 person-years of follow-up) and 42,526 men not diagnosed with HIV (269,281 person-years of follow-up) in the same age range (35 to 64 years). The men with HIV could contribute person-years to a non-PI group and to a PI group if they began PI therapy during follow-up, as many did. No one had a history of CHD or MI at the beginning of follow-up.

Rates of traditional risk factors at any time during follow-up proved similar in the HIV and non-HIV groups, except that men with HIV smoked more:

- Hypertension: 27 percent HIV, 34 percent non-HIV
- Hyperlipidemia: 23 percent HIV, 25 percent non-HIV
- Diabetes: 7 percent HIV, 9 percent non-HIV
- Ever smoked: 24 percent HIV, 13 percent non-HIV

From January 1996 through December 2003, men with HIV had significantly higher age-adjusted rates of both CHD and MI than men without HIV:

- CHD: 6.3 per 1,000 person-years HIV, 3.0 per 1,000 person-years non-HIV, P < 0.0001
- MI: 3.7 per 1,000 person-years HIV, 2.2 per 1,000 person-years non-HIV, P < 0.0001

CHD and MI rates proved higher among men taking PIs than among HIV-infected men not taking PIs, but not significantly so. When Klein figured age-adjusted CHD and MI rates according to length of PI exposure, he found that CHD incidence crept up from 5.9 per 1,000 person-years for men who took PIs fewer than two years to 8.8 per 1,000 person-years for those who took PIs from six to 7.9 years. That trend fell shy of statistical significance (P = 0.07).

The MI rate also climbed with added PI experience, but erratically. The age-adjusted MI rate measured 3.0 per 1,000 person-years for men with fewer than two years of PI experience, 4.6 with two to 3.9 years of PI experience, 3.7 with four to 5.9 years, and 5.0 with six to 7.9 years. This trend fell well short of statistical significance (P = 0.33).

Klein speculated that the lack of significant time trends for PI exposure could reflect the relatively short follow-up—a maximum of eight years and a median of four—or heightened clinician attention to risk factors, especially high lipids. (The French study, in contrast, found a higher MI risk after only 18 months of PI therapy.22) A proportional hazard regression analysis of Klein’s cohort did implicate PI therapy as an independent risk factor for both CHD (hazard ratio [HR] 3.37, P < 0.0001) and MI (HR 4.11, P < 0.0001).

Antiretroviral therapy did not raise the risk of hypertension in a 16,002-person analysis of the DAD collaboration [abstract 75]. But the US Women’s Interagency HIV Study (WIHS) did tie antiretrovirals to higher hypertension rates [abstract 741].

The DAD contingent consists of 11 cohorts in Europe, Australia, and the United States. Rodolphe Thiébaut (University Hospital Center, Bordeaux) offered two analyses—the first involving 16,002 people who had a median of three blood pressure readings over a median of 1.5 years [abstract 75]. In an adjusted model, type or duration of antiretroviral therapy did not influence blood pressure at cohort entry or boosts in blood pressure during follow-up. Four classic risk factors did independently raise the risk of a higher than predicted systolic blood pressure rise (≤5 mm Hg) throughout follow-up: male gender, older age, higher body mass index, and use of antihypertensives.

The second analysis focused on 8,341 people who had one normal blood pressure reading; 487 of them (6 percent) later had two consecutive readings topping 140/90 mm Hg. Antiretroviral therapy did not influence a new diagnosis of hypertension in this cohort. Four variables that did matter held little surprise: male gender, heftier body mass index, older age, and higher baseline blood pressure.

Ann Khalsa (University of Southern California, Los Angeles) and WIHS coworkers found no difference in hypertension prevalence or incidence between 2,057 HIV-infected women in the cohort and 569 “demographically similar” women without HIV infection [abstract 741]. But unlike the DAD researchers they did turn up evidence that longer antiretroviral therapy hikes the risk of hypertension.
The WIHS team defined hypertension as a diastolic pressure at or over 90 mm Hg, a systolic pressure at or over 140 mm Hg, current antihypertensive therapy, or self-reported hypertension. (DAD defined hypertension by the first three criteria but not the fourth.) The prevalence for both the HIV and non-HIV groups stood at 19 percent, while the incidence measured 47 percent in the HIV group and 46 percent in the non-HIV group. A multivariate analysis picked out seven classic factors that raised the risk of incident (newly diagnosed) hypertension and one protective factor (at the following relative risks [RR] and 95 percent CIs):

- Age 30 to 39 years (versus <30): RR 1.63 (1.18 to 2.24), P < 0.0001
- Age 40 to 49 years (versus <30): RR 2.67 (1.92 to 3.71), P = 0.003
- Age >50 years (versus <30): RR 5.22 (3.60 to 7.58), P < 0.0001
- African American (versus white): RR 1.42 (1.09 to 1.85), P = 0.01
- Smoking at two semiannual visits (versus no smoking): RR 1.49 (1.16 to 1.91), P = 0.002
- Smoking at three or more semiannual visits (versus no smoking): RR 1.32 (1.07 to 1.62), P = 0.01
- Body mass index ≥30 kg/m² (versus 20 to 24 kg/m²): RR 1.72 (1.43 to 2.08), P < 0.001
- Pregnancy: RR 0.56 (0.35 to 0.92), P = 0.02

A similar analysis of antiretroviral variables found that use of potent combinations and longer use of such regimens independently raised the risk of hypertension, whereas antiretroviral monotherapy lowered the risk:

- Potent antiretrovirals versus none: RR 1.26 (1.10 to 1.48), P = 0.01
- Potent antiretrovirals without AZT: RR 1.22 (1.03 to 1.45), P = 0.02
- Potent antiretrovirals at one semiannual visit: RR 1.32 (1.11 to 1.58), P = 0.02
- Potent antiretrovirals at two semiannual visits: RR 1.36 (1.12 to 1.65), P = 0.02
- Potent antiretrovirals at three or more semiannual visits: RR 1.51 (1.30 to 1.75), P < 0.0001
- Monotherapy versus no antiretrovirals: RR 0.76 (0.60 to 0.98), P = 0.03
- AZT versus no AZT: RR 0.81 (0.71 to 0.94), P = 0.004
- AZT monotherapy versus no antiretrovirals: RR 0.50 (0.35 to 0.72), P = 0.0001

The different conclusions DAD and WIHS reached about the impact of potent antiretrovirals on hypertension may reflect differences in the cohorts and length of follow-up. Both used similar definitions of prevalent and incident hypertension. The DAD cohort is much bigger than the WIHS cohort and includes both men and women. On the other hand, follow-up in DAD extends only to a median of 1.5 years, whereas the WIHS follow-up stretches all the way back to 1994 and 1995, the first years of enrollment.

Khalsa and WIHS colleagues thought hypertension might prove a long-term consequence of antiretroviral therapy because high blood pressure is one component of metabolic syndrome X. And many people taking antiretrovirals have one or more of the other three syndrome X features—obesity, insulin resistance or diabetes, and high lipids. Besides, she explained in an e-mail to IAPAC Monthly, a tenet of general medicine holds that the longer someone is obese, the greater their chance of getting diabetes or hypertension. This pathologic path seems especially likely among US women with HIV infection, who are often overweight or obese. So it also seemed likely, Khalsa added, “that duration of HIV-related metabolic dysfunctions would likely be related to development of hypertension.”

An earlier analysis of the all-male US Multicenter AIDS Cohort Study tended to bolster the WIHS findings. Taking a potent regimen for more than two years raised the risk of systolic (but not diastolic) hypertension 1.8 times in an analysis of data dating as far back as 1987. But HIV-infected men not taking antiretrovirals or taking one or two antiretrovirals had a lower hypertension risk than uninfected men.

Why did AZT and other monotherapies appear to have a protective effect? “We really do not have an explanation,” Khalsa e-mailed IAPAC Monthly. She suspects the finding may be anomalous because AZT had no protective effect when used in potent regimens. At any rate, renewed interest in monotherapy to exploit its antihypertensive potential seems unlikely.

As one descends from potentially mortal clinical outcomes (like heart attacks), to clinically crucial morbidities (like hypertension), to nebulous lab markers (like C-reactive protein, CRP), parsing the impact of potent therapies becomes tougher, but no less intriguing. Higher CRP numbers signal inflammation, a trait of uncontrolled HIV infection, and strongly predict coronary artery disease in general populations of men and women.26
Earlier work traced a firm link between higher CRP and a higher death risk in women with HIV.27 Tracking CRP readings in 99 people with well-controlled viremia while taking IDV in ACTG 372A, Keith Henry (University of Minnesota, Minneapolis) found stable or dwindling levels of the marker.

The CRP study subgroup was 87 percent male; 51 percent smoked, 14 percent had hypertension, and 10 percent had diabetes. Looking at all 99 people, Henry charted dwindling median CRPs when comparing pre-IDV levels (2.39 mg/L) to levels at IDV treatment month 42 (2.29 mg/L) and month 73 (1.72 mg/L), a nonsignificant trend. Focusing only on 50 people who had CRP measures at all three points, Henry did measure a significant ebb—2.75 mg/L before IDV, 2.19 mg/L at month 42, and 2.03 mg/L at month 73 ($P=0.02$). At the 42-month milestone, higher CRPs correlated with fewer months on IDV, along with ominous trends in coronary artery disease markers like fibrinogen and HDL-c ($P<0.05$). For men in the study group, those correlations were stronger ($P<0.01$).

These findings challenge results of a shorter and smaller study in which CRP levels did not drop significantly in 17 people who muted viral replication during the first year of antiretroviral therapy.28 The median CRP value in those people at the point of maximal suppression, 1.8 mg/L, came close to the 1.72 mg/L median seen in the IDV study at 73 months at therapy. Because so many factors may sway CRP levels in people with HIV infection, it may take a multivariate analysis in a large study to sort out the impact of antiretrovirals. But Henry’s study shores up the argument that the pluses of potent therapy—in this case dousing inflammation—still outweigh treatment’s cardiovascular minuses.

**Statins, fish oil, restitched arteries**

The big news on statin therapy for high cholesterol came not at the 11th CROI, but a few weeks later in a 4,162-person contest between pravastatin and atorvastatin.29 Among people already in the hospital for an MI or another acute coronary threat, 80 mg of atorvastatin daily lowered ominous low-density lipoprotein cholesterol (LDL-c) significantly more than 40 mg of pravastatin daily after an average two years of follow-up. Atorvastatin pushed median LDL-c down to 62 mg/dL (1.60 mmol/L) versus 95 mg/dL (2.46 mmol/L) with pravastatin ($P<0.001$) while trimming the risk of a composite morbidity/mortality endpoint by 16 percent compared with pravastatin ($P=0.005$).

The results were shockers for two reasons: Many assumed pravastatin would hold its own against atorvastatin in this head-to-head clinical endpoint comparison, and the low median LDL-c reached in the atorvastatin group lay far below the recommended goal (100 mg/dL) for people who already have serious heart problems.30 What the findings mean for people whose heart hasn’t sent them to the hospital yet remains uncertain, though that hasn’t stopped speculation.

Some cardiologists who talked to The New York Times believe “the study’s results [apply] to everyone at high risk” and perhaps “to everyone whose cholesterol levels are elevated.”31

What these results say about treating hyperlipidemia in people with HIV is even more murky. Before this trial, some HIV experts leaned toward pravastatin because it doesn’t interact with PIs, but others favored atorvastatin, thinking it’s the stronger statin. The ACTG and confreres from other groups recommend either atorvastatin or pravastatin when high cholesterol demands drug therapy.32 They believe pravastatin is safe in people taking PIs and that atorvastatin “can probably be used with caution, at low initial doses.” These experts add that neither statin consistently attains cholesterol goals30 that now may need updating.

Pravastatin and fenofibrate—alone or together—failed to help many antiretroviral-treated people reach lipid goals in ACTG A5087 [abstract 723]. Judith Aberg (Washington University, St. Louis) and colleagues signed up 174 people with LDL-c above 130 mg/dL and triglycerides above 200 mg/dL, randomizing 88 to start with fenofibrate (200 mg daily) and 86 with pravastatin (40 mg daily). They aimed for an LDL-c below 100 mg/dL in people with two or more cardiovascular risk factors and below 130 mg/dL in those with fewer risk factors. The triglyceride target was less than 200 mg/dL for people starting with 200 to 800 mg/dL and less than 400 mg/dL for people starting with triglycerides under 800 mg/dL and LDL-c above 35 mg/dL. After 12 weeks anyone who failed to reach these modified National Cholesterol Education Program (NCEP)30 composite goals added the other drug and continued treatment through week 48.

At week 12, Aberg counted only one composite responder in the fenofibrate group and four in the pravastatin group. The trial continued with 60 fenofibrate takers adding pravastatin and 63 pravastatin takers adding fenofibrate. At week 48 four people (7 percent) adding pravastatin to fenofibrate and two (3 percent) adding fenofibrate to pravastatin made the composite NCEP goal (Table 5).

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**Table 5. Lipid goals reached at 48 weeks with fenofibrate and pravastatin**

<table>
<thead>
<tr>
<th>Goal</th>
<th>Pravastatin added to fenofibrate* ($n=60$)</th>
<th>Fenofibrate added to pravastatin* ($n=63$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%) achieving goal</td>
<td>Median change from baseline (mg/dL)</td>
<td>Median change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Composite lipid goal</td>
<td>4 (7) -</td>
<td>2 (3) -</td>
</tr>
<tr>
<td>LDL-c</td>
<td>8 (13) -6</td>
<td>9 (14) -14</td>
</tr>
<tr>
<td>HDL-c</td>
<td>40 (67) +4.5</td>
<td>35 (56) +2</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>30 (60) -143.5*</td>
<td>28 (44) -66</td>
</tr>
</tbody>
</table>

*Second drug added after 12 weeks with the first drug.

Pravastatin 40 mg daily; fenofibrate 200 mg daily.

1 $P=0.019$ versus fenofibrate added to pravastatin.

Source: Judith Aberg, abstract 723.
Probably because fibrates tamp down triglycerides more than statins, giving fenofibrate first yielded significantly greater drops in absolute (P=0.019) and percentage (P=0.004) triglyceride levels. On the other hand, adding fenofibrate to pravastatin dimmed the LDL-c-lowering dint of pravastatin alone.

Alone or together, the drugs caused few problems. Four people dropped out during the first 12 weeks and three during the remaining 36. Rhabdomyolysis, the potentially fatal muscle wasting that combined statins and fibrates can cause, developed in no one. Despite the reassuring safety results, the ACTG team concluded that “more effective lipid-lowering treatments” are needed for people with HIV.

In the first double-blind, placebo-controlled, crossover trial of pravastatin (40 mg daily) in 18 men and two women taking PIs, eight weeks of the statin plus diet significantly lowered total cholesterol, LDL-c, non-HDL-c, LDL particle concentration, and small very low-density lipoprotein cholesterol when compared with eight weeks of diet plus placebo [abstract 77]. James Sosman (University of Wisconsin, Madison) also reported a trend toward improved endothelial function with pravastatin. Together, he concluded, these changes suggest reduced heart disease risk with pravastatin. But he speculated that the effect may have proved greater with atorvastatin.

Sosman mentioned the difficulty of recruiting people for this study because so many have switched from PIs to NNRTIs. But switching to EFV doesn’t remove the risk of baneful interactions with statins. A study of 28 people who added simvastatin (40 mg daily) or atorvastatin (10 mg daily) to standard-dose EFV for 14 days charted a 60 percent plunge in 24-hour simvastatin exposure and a 34.5 percent drop in total active atorvastatin [abstract 603]. EFV manages these feats by speeding the metabolism of both statins via the CYP3A4 enzyme. John Gerber (University of Colorado, Denver) suggested that some people taking EFV with one of these statins may need higher doses of the anti-lipid drug. But boosting statin doses should be tried only when drug levels can be monitored closely to prevent toxicity.

The meager benefits of pravastatin plus fenofibrate in Aberg’s ACTG study add to the urgency of finding effective anti-lipid strategies. Another randomized trial didn’t offer conclusive evidence that fish oil (omega-3 fatty acid) will be among them [abstract 724]. David Wohl (University of North Carolina at Chapel Hill) randomized 52 people to take the European fish oil product Coromega (about 3 g daily) plus counseling on diet and exercise or counseling alone for 16 weeks. Eight people dropped out before week four, so the comparison rests on 25 people taking fish oil and 19 getting only counseling. Triglycerides averaged 454 mg/dL in the fish oil group and 553 mg/dL in the counseling group. Baseline CD4 counts, viral load, and age were similar in the two study arms. Everyone had taken the same antiretrovirals for at least three months, and no one was taking a fibrate.

At week four mean triglycerides fell 19.6 percent with fish oil and rose 6.4 percent with counseling alone (P=0.049). But by week 16 the difference between groups had lost statistical significance (-17.7 percent versus -3.5 percent, P=0.134). At week four nine people (36 percent) taking fish oil had pared their triglycerides below 200 mg/dL compared with two people (11 percent) in the control arm (P=0.046). By week 16 six members of the fish oil group (27 percent) still had a triglyceride level below 200 mg/dL, while four (26 percent) had reached that mark in the counseling-only group (P=0.279). Self-reported adherence with fish oil was good. Wohl argued that the trends in this small study support larger trials of fish oil for HIV-infected people with high triglycerides.

What happens when diet, exercise, statins, fibrates, and fish oil fail to rein in runaway lipids and people with HIV need some coronary artery rerouting? A case-control study presented by Franck Boccara (Saint Antoine University Hospital, Paris) found that HIV-infected people who need percutaneous coronary intervention (PCI) do just as well as uninfected controls 12 months after surgery [abstract 740]. People with HIV who need coronary artery bypass grafting (CABG) had more complications than uninfected controls through 29 months of follow-up, but rates of death, new MI, or later PCI did not differ between CABG cases and controls.

The five-center analysis involved 44 HIV-infected people and 44 age- and gender-matched controls who had PCI from 1997 through 2003, and 19 HIV-infected people matched with 38 controls who had CABG. HIV infection had lasted an average of more than seven years, and most people needing PCI (84 percent) or CABG (74 percent) had used PIs. Cases matched controls closely in cardiovascular risk factors with a few exceptions: more high triglycerides, low HDL-c, unstable angina, and MI in the people with HIV infection, and more obesity and family histories of premature coronary artery disease or diabetes in the comparison group without HIV.

Comparing cases and controls 12 months after PCI, Boccara found statistically similar rates of:
Among people who underwent CABG, those with HIV had a significantly higher rate of major adverse cardiac setbacks within 29 months because of a higher re-CABG rate:

- Death: none in either group
- Major adverse cardiac events: 11 (25 percent) HIV and seven (16 percent) non-HIV ($P=0.27$)
- New MI: Four (9 percent) HIV and 0 non-HIV ($P=0.12$)
- Target lesion revascularization: seven (16 percent) HIV and three (7 percent) non-HIV ($P=0.18$)
- Target vessel revascularization: 0 HIV and four (9 percent) non-HIV ($P=0.12$)

Boccara concluded that “coronary revascularization using either PCI or CABG is feasible and safe in HIV-infected patients with multivessel disease.”

On the metabolic front, the biggest news came from Australia, where the Rosey trial offered firm evidence that rosiglitazone does not improve lipoatrophy in people with HIV, while it does pose lipid risks. From the United States, signals surfaced that fractures resulting from thin bones may be underreported and undertreated. Two groups had possibly good news for people with peripheral neuropathy—a high-dose capsaicin patch and marijuana both eased the pain.

**Not-so-rosy results with rosiglitazone**

In lab studies glitazones spur the growth of fat cells, even when PIs get added to the mix. But it didn’t work out that way in PI-treated people with lipoatrophy, according to results of the 48-week, randomized, double-blind, placebo-controlled Rosey study [abstract 79]. The trial appears to settle a debate sparked when one small, placebo-controlled trial found no limb fat gains with rosiglitazone, while another did.

Rosey was both bigger and longer than the earlier studies and had an 80 percent power to spot a 0.5-kg difference in limb fat between study groups after 48 weeks. Andrew Carr (St. Vincent’s Hospital, Sydney) randomized 108 people—106 of them men—with antiretroviral-induced lipoatrophy to take 4 mg of rosiglitazone or placebo twice daily for 48 weeks. The groups matched closely in three measures of limb fat, duration of NRTI and PI therapy, time since stopping d4T, CD4 count, and viral load.

People randomized to rosiglitazone improved significantly on three markers of insulin sensitivity, but they gained no more DEXA-measured limb fat than placebo takers (0.14 kg versus 0.18 with placebo). Many people in both groups had quit d4T, which may explain some or all of the fat gain. Both groups lost a few shavings of total lean mass and added less than a kilogram of trunk fat. Analyses of baseline variables teased out no limb fat differences between the glitazone and placebo groups among:

- People taking or not taking a PI
- People taking or not taking d4T or AZT
- People in the highest versus the lowest quartile of insulin resistance (HOMA) scores
- People with limb fat mass above or below 2.36 kg

Some had conjectured that the two earlier placebo-controlled trials reached different conclusions about limb fat gains with rosiglitazone because one enrolled only insulin-resistant people while the other did not. Rosey’s results suggest that baseline insulin resistance has nothing to do with limb fat changes in people taking this insulin sensitizer.

Rosciglitazone inflated the toxic toll in people who took it in this trial, as it had in earlier studies. Triglycerides rose by an average 0.9 mmol/L (80 mg/dL) by week 48 ($P=0.03$) and cholesterol climbed by 1.5 mmol/L (58 mg/dL, $P=0.001$).

Because the study group consisted almost entirely of men, Carr and colleagues noted that rosiglitazone’s effects on peripheral fat in women and children remain unknown. The same holds true for people not taking PIs or NRTIs. The drug certainly has value as an insulin sensitizer, and plenty of people taking antiretrovirals need to counter insulin resistance. Glitazones also lower liver fat content. But as Carr cautioned in his paper on the trial, “any use [of rosiglitazone] for insulin resistance or type 2 diabetes in lipoatrophic HIV-infected patients will need to take into consideration the adverse lipid effects we noted.”

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**LIPO, BONES, AND NERVES**

**A 48-week placebo-controlled trial of rosiglitazone found that the insulin-sensitizing drug did not promote limb fat gains but did boost cholesterol and triglycerides.**
Long-term low-dose rhGH

No one doubts that recombinant human growth hormone (rhGH) reverses another feature of HIV lipodystrophy, central fat buildups. The drawbacks with this drug, besides its high cost, are its toxicity and transient effect on fat: As soon as people stop taking rhGH, the fat comes back. Both of these problems might be overcome—or at least minimized—by an ultralow dose that people can take more consistently. A 36-week extension of the STARS trial, presented by Donald Kotler (Columbia University, New York), suggested that only 1 mg daily is enough to maintain central fat drops wrought by a higher dose [abstract 80].

STARS started with 142 people burdened by too much trunk fat, including visceral fat. Men had a waist-to-hip ratio above 0.95 and women above 0.90. They took 4 mg of rhGH daily or every other day, or placebo, for 24 weeks. Most continued through week 36 after being randomized to 2 or 4 mg daily. The final randomization assigned 81 people to take 1 mg daily and 46 to take 2 mg daily from week 36 to week 60. Only eight people dropped out after the final randomization.

Counting back to STARS day 1, people taking either 1 or 2 mg in the final phase had significant drops in:

- DEXA-measured trunk fat: 9.5 to 8.4 kg with 1 mg; 9.8 to 8.4 kg with 2 mg
- Non-HDL-c: 175.6 to 154.4 mg/dL with 1 mg; 172.1 to 148.3 mg/dL with 2 mg
- Total cholesterol: 213.0 to 196.1 mg/dL with 1 mg; 209.2 to 190.7 mg/dL with 2 mg

Insulin area under the curve measured by glucose tolerance testing did not change significantly over the 60 weeks. No one had diabetes at baseline before starting rhGH. People taking the 2-mg dose had a higher rate of arthralgia than those taking 1 mg (12.5 versus 5.7 percent) during the final 24 weeks of the trial. Kotler called for further study of the 1-mg maintenance dose.

More on the mechanisms of atrophy

On the basis of cohort study results, Simon Mallal and coworkers (Royal Perth Hospital, Australia) proposed a synergistic effect of NRTIs and PIs in the evolution of lipodystrophy. Work by Patrick Mallon (University of New South Wales, Sydney) appeared to explain why drugs from these two classes double up to downsize subcutaneous fat [abstract 76].

A seminal study in this field implicated downregulation of PPAR-gamma in lipodystrophy. In that study people with scant PPAR-gamma protein were all taking PIs, while cell studies suggested NRTIs don’t affect this crucial receptor. But Mallon showed that if you look at those cells in people—instead of on lab dishes—NRTIs do plenty. He gave d4T/3TC or AZT/3TC for six weeks to 20 healthy volunteers without HIV infection. After a washout the volunteers switched to the opposite NRTI duo.

Lipids, glucose, insulin, lactates, and limb fat did not change during the six-week drug courses. But nuclear expression of PPAR-gamma in fat cells dropped 51 percent during the first two weeks of therapy ($P=0.002$), more so with d4T/3TC than with AZT/3TC, but not significantly so. At the same time, mitochondrial gene expression fell with both regimens. Notably, these changes appeared in people without HIV and before any NRTI-induced changes in fat or metabolic measures. Mallon proposed that NRTIs’ impact on PPAR-gamma could explain the apparent lipoatrophic synergy between these drugs and PIs. He also suggested that mitochondrial gene expression may prove a better marker of mitochondrial toxicity than mitochondrial content in cells.

A post hoc analysis of data from trials comparing once-daily extended-release d4T (d4T-XR) with standard twice-daily d4T suggested that the new formulation leads to less lipatrophy than the old [abstract 722]. Mustafa Noor and Christopher Dezii (Bristol-Myers Squibb) looked back at variables that may influence lipodystrophy in 877 people from these studies who had pretreatment triglyceride readings. No one had antiretroviral experience before starting the trials, which included treatment with 3TC and EFV. Follow-up lasted a median of 116 weeks with d4T-XR and 114 weeks with the twice-daily formulation.

In a multivariate analysis of investigator-defined lipodystrophy, Noor and Dezii pinpointed two factors that lowered the risk of atrophy and one that raised the risk at the following odds ratios (OR) and 95 percent CIs:

- Pretreatment triglycerides below 200 mg/dL: OR 0.523 (0.292 to 0.935), $P=0.029$
- Age 40 or younger: OR 0.454 (0.278 to 0.743), $P=0.002$
- Old d4T versus XR-d4T: OR 1.975 (1.252 to 3.117), $P=0.003$

Extended-release d4T had the biggest protective effect relative to twice-daily d4T in people with triglycerides at or above 200 mg/dL. Among people older than 40 with high triglycerides, lipodystrophy developed in 33.3 percent taking twice-daily d4T and 12.5 percent taking d4T-XR. Among people 40 years old or younger with high triglycerides, lipodystrophy appeared in 21.9 percent taking twice-daily d4T and 4.4 percent taking d4T-XR. Gender, race, and baseline glucose, body mass index, waist circumference, viral load, and CD4 count did not affect the emergence of peripheral fat wasting.

A slimmer risk of lipodystrophy with d4T-XR makes sense because the new once-a-day formulation yields lower peak concentrations than the twice-daily drug. But the Bristol-Myers Squibb team pointed out several limitations of this study—investigator-defined (rather than objectively measured) lipodystrophy, collection of data from the unblinded study phase, and potential confounders like smoking and other lifestyle habits and treatment with lipid-lowering and insulin-sensitizing drugs.
Broken bones: Underreported and poorly managed?

A study of fragility fractures in people with HIV by Grace McComsey (Case Western Reserve University, Cleveland) and colleagues from eight other large HIV clinics suggested that broken bones are underreported and poorly managed in HIV-infected people [abstract 743]. About half of those who had DEXA scans in this retrospective analysis had osteopenia, not osteoporosis.

Digging through records of about 8,600 people, McComsey and coworkers turned up 49 fractures that happened after minimal or no trauma. The earliest dated to February 1991, but all the others happened after October 1997. Median age at the time of fracture measured 45 years and ranged from 25 to 75 years. About half of these people smoked, 15 percent reported drinking too much alcohol, and seven had used steroids. The median body mass index was low by US standards—23.29 kg/m²—in these 37 men and 12 women (range 15.81 to 32.25 kg/m²). Two people had never taken antiretrovirals. The median duration of antiretroviral therapy stood at 37 months and the median PI duration at 25 months.

Among 10 people who had lower-spine DEXAs, only four had osteoporosis (t-score < -2.5), while five had osteopenia (t-score -1 to -2.5). Among 10 people who had hip DEXAs, four had osteoporosis and four osteopenia. Most fractures involved vertebrae (25) or legs (15). Only 19 of 49 people had some bone-related therapy, which McComsey rated “not reaching the standard of care of fragility fractures in the general population.” After a median follow-up of 10 months after a fracture, nine of 36 people (25 percent) snapped another bone, and seven of these breaks involved different bones.

The retrospective nature of the study prevented McComsey and colleagues from ruling out non-HIV causes of broken bones in these people. Nevertheless, they believe their findings show that “further education will continue for another year.

Low bone density raises even greater concern in children with HIV, who may face a lifetime of fracture threats. A study of 43 children who had two lumbar spine DEXA scans separated by 10 to 23 months disclosed a high rate of osteopenia but little or no progression between the two scans [abstract 745]. That result contradicts, in part, a case-control study of 32 children with at least 40 months of antiretroviral experience than in 381 comparably aged controls without HIV. Although the annual gain in the HIV group’s spine density matched normal gains, their whole-skeleton bone growth significantly lagged normal gains (P < 0.04). Significantly higher bone turnover marker levels in the children with HIV confirmed their abnormal bone metabolism.

A study that randomized 18 people to take alendronate (70 mg weekly) plus calcium and vitamin D and 23 to take calcium and vitamin D alone found a significant drop in the bone resorption marker N-telopeptide in the alendronate group (11,559 to 1,194 pM/L) but not in controls after 52 weeks [abstract 742]. Everyone began treatment with a t-score below -1.0. Giovanni Guaraldi (University of Modena and Reggio Emilia, Italy) reported that lumbar spine density rose by 4 percent with alendronate (P = 0.004), but femoral neck density fell by 0.5 percent (P = 0.05). Follow-up will continue for another year.

Progress in easing neuropathy pain

Capsaicin—the stuff that makes hot peppers hot—has had mixed success as a remedy for neuropathy pain in people with HIV. Capsaicin cream itself causes some pain, it must be applied several times a day, and the dose must be raised slowly. So adherence has been a problem. David Simpson (Mount Sinai Medical Center, New York) may have found a solution to these problems—make the first dose really high, and make it the only dose for weeks [abstract 490]. The downside of this strategy is that it may worsen neuropathic pain in the first few days; the upside is that a single treatment may last three months or more.

Simpson and colleagues at two other sites recruited nine men and three women with moderate or severe neuropathic pain in both feet, four of whom were taking NRTIs that can cause neuropathy. The protocol prohibited use of other topical medications, but people could continue systemic pain relievers they had taken for at least three weeks.

But the clinical import of that finding is unclear because PI therapy didn’t correlate with five markers of bone turnover, while it did correlate with one (calcium/creatinine ratio above 0.2).

The published study found significantly lower bone mineral densities in 32 children with at least 40 months of antiretroviral experience than in 381 comparably aged controls without HIV. Although the annual gain in the HIV group’s spine density matched normal gains, their whole-skeleton bone growth significantly lagged normal gains (P < 0.04). Significantly higher bone turnover marker levels in the children with HIV confirmed their abnormal bone metabolism.

A study that randomized 18 people to take alendronate (70 mg weekly) plus calcium and vitamin D and 23 to take calcium and vitamin D alone found a significant drop in the bone resorption marker N-telopeptide in the alendronate group (11,559 to 1,194 pM/L) but not in controls after 52 weeks [abstract 742]. Everyone began treatment with a t-score below -1.0. Giovanni Guaraldi (University of Modena and Reggio Emilia, Italy) reported that lumbar spine density rose by 4 percent with alendronate (P = 0.004), but femoral neck density fell by 0.5 percent (P = 0.05). Follow-up will continue for another year.

Progress in easing neuropathy pain

Capsaicin—the stuff that makes hot peppers hot—has had mixed success as a remedy for neuropathy pain in people with HIV. Capsaicin cream itself causes some pain, it must be applied several times a day, and the dose must be raised slowly. So adherence has been a problem. David Simpson (Mount Sinai Medical Center, New York) may have found a solution to these problems—make the first dose really high, and make it the only dose for weeks [abstract 490]. The downside of this strategy is that it may worsen neuropathic pain in the first few days; the upside is that a single treatment may last three months or more.

Simpson and colleagues at two other sites recruited nine men and three women with moderate or severe neuropathic pain in both feet, four of whom were taking NRTIs that can cause neuropathy. The protocol prohibited use of other topical medications, but people could continue systemic pain relievers they had taken for at least three weeks.
First lidocaine 4 percent cream, a topical anesthetic, is swabbed onto the affected area and left for an hour. Then the NGX-4010 patch (Capsaicin Dermal Patch, 640 µg/cm²) does its work for one hour. Finally the treated area gets doused with a cleansing gel, soap, and water.

All 12 study participants completed treatment, though one withdrew from follow-up for personal reasons and another stopped coming back for checkups. Using a pain score ranging from 0 to 10, Simpson recorded an average drop of 40 percent (95 percent CI -60.7 to -18.7 percent, \( P = 0.003 \)) over 12 weeks of follow-up. One person felt no improvement, and one thought the pain worsened. Eight people (67 percent) met the study response criterion—at least a 30 percent drop in pain. Results proved similar with a “pain now” score and “worst pain over the past 24 hours.”

Eight people had pain scores at least 30 percent higher than baseline levels during the first 48 hours, and seven needed oxycodone to blunt this early sting. Three people used hydrocodone during the first five days after treatment. One 48-year-old man endured “severe pain and paresthesia” after treatment. Simpson noted that his “ongoing use” of a fentanyl patch and oxycodone “likely precluded the ability to relieve treatment-related discomfort with orally administered narcotics.” A larger randomized trial of the high-dose capsaicin patch is under way.

A poster just down the aisle from Simpson’s underscored the paradoxical palliation with this pain inducer. A noncomparative trial of marijuana for people with HIV-related neuropathy used a heat-capsaicin model of hyperalgesia (extreme sensitivity to painful stimuli) to confirm that cannabis can quench neuropathic flames [abstract 496].

Cheryl Jay (University of California, San Francisco) recruited 14 men and two women with neuropathy due to HIV, NRTIs, or both. They had taken the same antiretrovirals for at least eight weeks and the same pain medications, if any, for at least two weeks. Everyone had a pain score of 30 or higher on a 100-point visual analog scale. All study participants had used marijuana before; none were substance abusers.

After recording baseline pain scores for a week, these 12 people checked into the hospital for seven days and smoked one marijuana cigarette (3.56 percent THC) three times daily. Ten of 16 people (62.5 percent) had at least a 30 percent drop in average daily pain on the visual analog scale, the study’s primary endpoint.

This result correlated well with quelling of heat- and capsaicin-induced hyperalgesia. Because of the open-label design of this trial and because everyone had used marijuana before, these findings must be confirmed in a randomized, double-blind, placebo-controlled trial. Such a study is up and running.

A trial that randomized 40 people with HIV neuropathy to take a micronutrient supplement or placebo for 12 weeks found no significant pain advantage with the supplement [abstract 494]. All were taking either ddl, d4T, or both. The supplement included three antioxidants—400 mg of alpha lipoic acid, 1,000 mg of acetyl L-carnitine, and 1,200 mg of N-acetyl cysteine—plus 30 vitamins and minerals. The study rationale rested on the role of antioxidants in preventing mitochondrial toxicity.

John Kaiser (University of California, San Francisco) reported a 42 percent improvement on a linear pain scale and a 29 percent gain in quality of life measurements with the supplement, but these changes did not differ significantly from gains in the placebo group. Nor did the groups differ in neurologic exam results. People taking the supplement averaged a CD4 jump of 65 cells/mm³ over the 12 weeks, while the placebo group lost an average 6 cells/mm³ (\( P = 0.03 \)). Kaiser did not speculate on potential mechanisms behind this difference. The micronutrient had no ill effects on fasting glucose, insulin, cholesterol, triglycerides, serum lactate, or alanine aminotransferase.

People who predicted that strong three-drug regimens would turn HIV into a chronic disease turned out to be right. Which is not to say that living 20, or 40, or 60 years with a disfiguring chronic disease is any way to live. Even “good news” stories that emerge from HIV meetings often seem more black cloud than silver lining. For example, three studies presented at the 11th CROI (reviewed in the April 2004 IAPAC Monthly) confirmed that liver transplants are working well in people with HIV. But how many of those people would be worrying away days on transplant waiting lists if they didn’t have HIV to complicate their HCV?

Similarly, an important study by Kaiser-Permanente investigators showed that antiretroviral-treated people now endure standard surgeries as well as people without HIV (see note 40 for details). But maybe some of those bypass grafts and hip replacements wouldn’t be needed if people never caught this chronic disease. Meanwhile, living longer with the retrovirus, HIV Outpatient Study investigators told us, has turned a lot of so-called non-AIDS cancers into big problems for otherwise hale survivors (see note 41 for details).
This line of reasoning can sound a lot like quibbling when one considers the alternative to surviving HIV long enough to get avascular necrosis and need new hips. But battling a chronic disease like hypertension probably looks like a good bargain to someone awaiting hip replacement with well-controlled HIV. Even dealing with needles for diabetes may look easy to the ENF injector with lipoatrophy and unruly lipids, who may get diabetes anyway.

In the same way, reminding antiretroviral-taking Westerners how much better off they are than the untreated millions elsewhere qualifies as a candescent example of cold comfort. But those of us without HIV—especially those whose research or ruminating or writing mostly involves antiretrovirals and their nettles—can stand reminding that a whole world lives (and dies) without wasting a minute of worry over which PI unglue glucose metabolism. And the 11th CROI offered two rich reminders that the world of AIDS can seem both a very small world and a hopelessly large one.

\[i. \text{Hemoglobin}\]

Hemoglobin, the red blood cell protein that totes oxygen from lung to tissue, also turns out to be a first-class predictor of HIV disease progression and death. It does that whether you live in Baltimore, Maryland, or Maputo, Mozambique.

Richard Moore and Jeanne Keruly (Johns Hopkins University, Baltimore) reckoned the risk-predicting prowess of low hemoglobin along with CD4 counts in 1,718 people who began potent antiretrovirals in the Johns Hopkins clinic since January 1996 [abstract 561]. Their study group was 73 percent African American and 75 percent male. About 30 percent picked up HIV during gay sex, 27 percent during straight sex, and 22 percent while injecting drugs. In a multivariate analysis adjusted for gender, race, HIV risk group, CD4 percent, and viral load, Moore and Keruly found that low hemoglobin predicted a new AIDS diagnosis or death in the six months after measurement as robustly as low CD4s:

- Hg <10 g/dL: adjusted incidence rate ratio (IRR) 4.6 (95 percent CI 1.3 to 6.2)
- Hg 10.1 to 11 g/dL: IRR 3.4 (2.3 to 5.1)
- Hg 11.1 to 12 g/dL: IRR 2.4 (1.6 to 3.6)
- Hg >12 g/dL (reference): 1.0
- CD4 <50 cells/mm³: IRR 3.7 (1.8 to 7.6)
- CD4 50 to 100 cells/mm³: IRR 2.8 (1.4 to 5.7)
- CD4 101 to 200 cells/mm³: IRR 1.9 (1.0 to 3.6)
- CD4 201 to 350 cells/mm³ (reference): 1.0

Moore and Keruly concluded, “Hemoglobin may be a surrogate marker of immune activation or cytokine-mediated processes not fully accounted for by the CD4, HIV-1 RNA level and other measures.”

The Community of Sant’Egidio in Rome has run a free HIV care and antiretroviral therapy program in Mozambique since February 2002. Leonardo Palombi (University of Tor Vergata, Rome) reported that the program in Maputo province includes 510 women, 292 men, and 215 children [abstract 148]. About half of the adults and one third of the children met criteria for antiretroviral therapy. After a median follow-up of 290 days in treated adults and 140 days in untreated adults, a multivariate analysis showed that starting antiretroviral therapy was the only better predictor of survival (odds ratio 2.98) than hemoglobin (odds ratio 2.34). Viral load (odds ratio 1.74) and CD4 count (odds ratio 1.41) proved less potent predictors of short-term survival.

Research involving 273 gay men in the Multicenter AIDS Cohort Study found that rapid drops in total lymphocyte count and hemoglobin could strengthen World Health Organization (WHO) guidelines for starting antiretrovirals in places that can’t afford CD4 counts [abstract 869]. The study also rated quickly falling hemoglobin a stronger marker than quickly falling total lymphocytes. Bryan Lau (Johns Hopkins School of Public Health, Baltimore) and colleagues in Chicago, Pittsburgh, and Los Angeles charted total lymphocytes and hemoglobin in men who had at least four AIDS-free visits after being infected with HIV. Defining a rapid total lymphocyte drop as at least 33 percent yearly and a rapid hemoglobin drop as at least 11.6 percent yearly, they figured the following relative hazards (RH) for disease progression:

- Rapid total lymphocyte decline (adjusted for RNA): RH 1.84 ($P=0.0067$)
- Rapid hemoglobin decline (adjusted for RNA): RH 2.34 ($P=0.0003$)
- Rapid total lymphocyte decline (adjusted for RNA and CD4): RH 1.41 ($P=0.12$)
- Rapid hemoglobin decline (adjusted for RNA and CD4): RH 1.72 ($P=0.023$)

Lau and coworkers believe their findings “support supplementing the WHO guidelines so that individuals are monitored for marker declines in addition to low [total lymphocyte count] levels.” Current WHO guidelines suggest starting therapy for people with WHO stage II or III disease and a total lymphocyte count under 1,200 cells/mm³.

After the 11th CROI, the WIHS group published an analysis of 873 US women who had hemoglobin, total lymphocytes, CD4 cells, and delayed-type hypersensitivity (DTH) responses measured within the year before starting antiretroviral therapy. Using three different models to predict progression to AIDS and death, they isolated six independent risk factors:
The WIHS team calls for further study of total lymphocyte count, hemoglobin, and DTH response as thresholds for starting antiretrovirals “in resource–limited settings.” But Bryan Lau and others think resource–rich settings may have something to gain too. They noted in their poster that both total lymphocytes and hemoglobin started their fast slide before people had symptoms of AIDS, while CD4 counts stood between 200 and 350 cells/mm³. No one suggests tossing out CD4 counts in countries that can pay for them. But for an extra pittance to track total T cells and hemoglobin, Lau and colleagues suggested, even people with tip–top public or private insurance could get another angle on when to start therapy.

**ii. Henan**

China’s Henan province lies about 700 miles north of Hong Kong and about 400 miles west of Shanghai. But it’s a world away from the cosmopolitan flare and the postcapitalist lucre of those megalopolis. For the poor farmers and villagers of Henan, the chance to get an economic leg up came not from shuffling financial instruments or recycling the West’s scrap, but in recycling their own blood. For about US$5 per visit in places like Sishui and Pingdingshan, they sold blood—again and again—to raise money to pay school fees or buy TVs. While they rested in the collection centers, pooled the blood, skimmed off the saleable parts, and reinfused the pooled leftovers so people could come back quickly for another sale. With that kind of scheme, it took only a little HIV to infect thousands.

In what may be local clinicians’ first report on Henan’s HIV epidemic outside of China, Y. He (Zhengzhou No. 6 People’s Hospital, Henan) set HIV prevalence in the province at 10,895 by the end of last year [abstract 573]. But that number will grow fast if these clinicians are right about the one–year rate of new infections transmitted from mothers to newborns—31.5 percent.

The poster focused on 72 boys and 16 girls, 41 of whom (47 percent) became infected via blood transfusions and 38 of whom (43 percent) got HIV from their mothers. Twelve had AIDS within one year of infection and 68 within five years. The Zhengzhou doctors are treating 17 children (19 percent) with antiretrovirals and 22 (25 percent) only with drugs for opportunists. The other 49 (56 percent) take no drugs because of “financial problems.” Since most children receive no treatment, these clinicians add, “the morbidity and mortality rate will [be] increasing in China.”

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**References and Notes**

18. This poster can be scrutinized at http://www.tibotec.com. Click on “Conferences,” then on “More Information” below “11th Conference on Retroviruses.”


40. This case-control study presented by Michael Horberg (Kaiser-Santa Clara, California) compared 295 people with HIV who had surgery and 295 seronegative controls matched for age, gender, and type, year, and location of surgery [abstract 82]. Horberg and colleagues tracked both groups for a year or more after they underwent appendectomy, coronary artery bypass surgery or valve replacement, mastectomy, cholecystectomy, hip or knee replacement or arthroplasty, or hernia repair. They found no significant difference in rates of postsurgical complications (12.2 percent in the HIV group versus 9.8 percent) or mortality. HIV-infected people who had surgery with a viral load above 10,000 copies/mL had more complications than those with a lower viral load (23 versus 8 percent, \( P = 0.009 \)), a finding that led Horberg to suggest that getting viral loads under 10,000 copies/mL “might improve surgical outcomes.” But he stressed that “HIV status should not by itself be a criterion for surgical consideration.”

41. Comparing cancer rates in two HIV Outpatient Study (HOPS) and three general-population cohorts, Pragna Patel (Atlanta, Georgia) found that people with HIV have a significantly higher incidence (new diagnosis rate) of several cancers that don’t fit in the AIDS definition [abstract 81]. An analysis adjusted for age, race, smoking, and gender found a significantly higher incidence of lung cancer, Hodgkin disease, head and neck cancer, melanoma, and anorectal cancer in the Chicago HOPS cohort than in two non-HIV groups in Cook County and Illinois from 1992 to 2002. Comparing non-Chicago HOPS cohort members with a national cancer registry, Patel found a significantly higher incidence of the same cancers except head and neck cancer in the HIV group. New diagnoses of two AIDS-defining cancers (Kaposi’s sarcoma and cervical cancer) but not another (non-Hodgkin lymphoma) dropped in the HOPS cohort after potent antiretroviral therapy arrived in 1996.

Pharmacotherapy

Pharmacodynamic effects of zidovudine 600 mg once/day versus 300 mg twice/day in therapy-naive patients infected with human immunodeficiency virus

Ruane PJ et al.

STUDY OBJECTIVE: To compare the virologic activity of zidovudine monotherapy administered as 600 mg once/day versus 300 mg twice/day. DESIGN: Phase II, randomized (1:1), open-label study. SETTING: 13 medical centers in the United States. PATIENTS: Thirty-two antiretroviral-naive patients infected with human immunodeficiency virus (HIV). INTERVENTION: Patients were administered either zidovudine 600 mg every 24 hours (16 patients) or 300 mg every 12 hours (16 patients) for 13 days. MEASUREMENTS AND MAIN RESULTS: Plasma HIV-1 RNA concentration was measured daily. Study end points were between-group differences in change from baseline of log_{10} transformed HIV-1 RNA and in rates of viral load decline measured by the slope of HIV-1 RNA over time. At baseline, mean HIV-1 RNA was similar in the once/day and twice/day groups (4.33 and 4.40 log_{10} copies/ml respectively). At day 14, a trend toward lower mean reduction in HIV-1 RNA from baseline was observed in the once/day group (-0.585, 95% confidence interval [CI] -0.728 to -0.442 log_{10} copies/ml) compared with the twice/day group (-0.849, 95% CI -1.067 to -0.630 log_{10} copies/ml, p=0.056). Viral load reduction also tended to be slower in the once/day group, as indicated by the smaller slope of viral load decline in the once/day group than in the twice/day group during days 1-14 (-0.045 vs -0.065 log_{10} copies/ml/day, p=0.065). Both zidovudine regimens were similarly well tolerated. CONCLUSION: Zidovudine 600 mg once/day has antiviral activity, although less pronounced and more slowly achieved than that seen with zidovudine 300 mg twice/day. No differences were observed between the two treatment groups with respect to safety profile or tolerability.


Journal of Infectious Diseases

Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and -experienced patients coinfected with HIV-1 and hepatitis B virus

Dore CJ et al.

BACKGROUND: Coinfection with human immunodeficiency virus type 1 (HIV-1) increases the risk of hepatitis B virus (HBV)-associated progressive liver disease. Lamivudine has potent activity against both HIV-1 and HBV; however, lamivudine-resistance mutations in HBV frequently develop. METHODS: Substudies of the safety and efficacy of tenofovir disoproxil fumarate (tenofovir DF) for patients coinfected with HIV and HBV were undertaken within two phase 3 randomized controlled trials involving antiretroviral therapy-experienced (study 907) and -naive (study 903) HIV-infected populations. Inclusion criteria were detection of hepatitis B surface antigen, an HBV DNA level >106 copies/ml at baseline, and HBV DNA specimens available at week 24 (study 907) and week 48 (study 903), RESULTS: In study 907, the mean decrease in HBV DNA was 4.9 log_{10} after 24 weeks for 10 patients randomized to receive tenofovir DF, compared with a mean increase of 1.2 log_{10} for two patients randomized to receive placebo (P=0.041). The mean decrease in HBV DNA during tenofovir DF treatment was similar for patients with wild-type (5.3 log_{10}) and lamivudine-resistant (4.6 log_{10}) HBV strains. In study 903, the mean decrease in HBV DNA was 3.0 log_{10} after 48 weeks, for six patients randomized to receive lamivudine, compared with 4.7 log_{10} for five patients randomized to receive lamivudine and tenofovir DF (P=0.055). Four patients developed tyrosine-methionine-aspartate-aspartate mutations, all in the lamivudine-only treatment arm. CONCLUSION: Tenofovir DF has potent anti-HBV efficacy in antiretroviral therapy-experienced and -naive individuals coinfected with HIV and HBV.


HIV Medicine

The high cost of medical care for patients who present late (CD4 <200 cells/mL) with HIV infection

Krent: HB et al.

OBJECTIVE: To compare the direct costs of medical care in the year following HIV diagnosis for patients who present with a CD4 count <200 cells/mL (late presenters) and those who present with a CD4 count >200 cells/mL (early presenters). METHODS: Direct costs (ie, drugs, laboratory tests, outpatient care, inpatient care, and home care) for the 12 months following HIV diagnosis, sociodemographic data and clinical data were collected for all patients presenting for HIV care in Southern Alberta, Canada, between April 1996 and April 2001. Mean costs are presented as costs in 2001 Canadian dollars. RESULTS: Thirty-nine percent of 241 patients presented with a CD4 count <200 cells/mL. The mean costs for late presenters were more than twice as high as those for early presenters (ie, $18,448 vs $8,455, respectively). Late presenters were more likely to be older, male and black, and to have a risk activity of men having sex with men (MSM) or heterosexual contact (P<0.05). However, the large difference in mean costs cannot be attributed to differences in characteristics. When characteristics were statistically held constant, the estimated excess cost of late presentation was almost unaffected, at $9,723 (z=5.6). Repeating the analysis using disaggregated costing categories suggested that the difference in total costs was largely attributable to differences in HIV-related hospital care costs, which were 15 times higher for late presenters.

CONCLUSIONS: Direct care costs in the year following HIV diagnosis were more than 200 percent higher for patients who presented late. This difference could not be attributed to differences in patient characteristics. Most costs were attributable to HIV-related hospital care costs and the immediate initiation of antiretroviral therapy. While early diagnosis in those at risk for HIV remains medically important, the short-term economic impact is also substantial.


Obstetrics & Gynecology

Trends in pregnancy rates among women with human immunodeficiency virus

Blair JM et al.

OBJECTIVE: To describe factors associated with pregnancy and trends in pregnancy rates among women with human immunodeficiency virus (HIV) before and after the release of US Public Health Service guidelines for the use of zidovudine and the increased availability of highly active antiretroviral therapy. METHODS: Human immunodeficiency virus (HIV)-infected women aged 15 to 44 years who were enrolled in the Adult/Adolescent Spectrum of HIV Disease Project, a medical records cohort study of HIV-infected persons conducted in more than 100 US healthcare facilities. RESULTS: Among 8,857 women, there were 1,185 incident pregnancies during 21,617 person-years of follow-up from 1992 through 2001. Pregnancy rate at enrollment was 16%; thereafter, an average of 5.5 percent of women became pregnant annually. Pregnancies were more likely to occur in women aged 15 to 24 years (adjusted rate ratio [RR] 9.2; 95 percent confidence interval [CI] 7.4, 11.3) and 25 to 34 years (adjusted RR 4.0; 95 percent CI 3.3, 4.9) than in women aged 35 to 44 years. Pregnancies were less likely to occur in women with a history of AIDS-opportunistic illness (adjusted RR 0.4; 95 percent CI 0.3, 0.5) or a CD4 count below 200 cells/mL and no opportunistic illness (adjusted RR 0.6; 95 percent CI 0.5, 0.7) than in women with HIV but not AIDS. Higher rates of pregnancy were observed for women prescribed highly active antiretroviral therapy (adjusted RR 1.3; 95 percent CI 1.0, 1.6) than women prescribed other regimens of antiretroviral therapy. There were significantly higher rates of pregnancy during 1997 through 2001. CONCLUSION: The increase in pregnancy rates during the era of widespread use of highly active antiretroviral therapy illustrates the continued need for comprehensive prevention and treatment services.

Focus on Hepatitis

Weight-based versus fixed-dose peginterferons

Thomas Shaw-Stiffel

Conservative estimates indicate that at least 3 million Americans are chronically infected with the hepatitis C virus (HCV), but despite an improved awareness of this condition, perhaps as few as 200,000 have been diagnosed up until now. As a result, the US National Institutes of Health (NIH) projects that during the coming 20 years there will be a four-fold increase in the detection rate of HCV.

Already, chronic HCV infection has become the leading cause of liver disease in the United States. In 20 to 30 percent of HCV-infected patients, progressive liver damage from HCV leads to cirrhosis, which is often complicated by ascites, encephalopathy, coagulopathy, and/or hepatocellular carcinoma.

The current mortality rate from HCV cirrhosis is 10,000 to 12,000 deaths per year, but according to the NIH, this is expected to triple during the next two decades. Hepatitis C virus-related cirrhosis has become the primary reason for liver transplantation in the United States, with almost universal recurrence post-transplant.

Fortunately, in the past few years, therapeutic advances to eradicate HCV have made steady gains. With the latest combination treatment using pegylated interferon (PEG-IFN) and ribavirin (RBV), overall 50 percent to 60 percent of patients with chronic HCV infection can expect to achieve a sustained virologic response (SVR), which is often complicated by ascites, encephalopathy, coagulopathy, and/or hepatocellular carcinoma.

The primary advantage of PEG-IFN α-2a and ribavirin (RBV) is that it can be as high as 70 percent to 80 percent, or even higher in patients who are the most compliant with taking their HCV medications (eg, those who take 80 percent or more of their medications for 80 percent or more of the recommended duration of treatment).

Currently, there are two types of combination therapy (PEG-IFN plus RBV) approved by the US Food and Drug Administration (FDA) to treat chronic HCV: 1) PEG-IFN α-2a and ribavirin tablets; and 2) PEG-IFN α-2b and ribavirin capsules.

Retrospective analyses of prior studies suggest that the likelihood of achieving an SVR correlates closely with the amount of RBV the patient had taken based on his/her body weight. This led to the important concept of “weight-based dosing” (WBD). The pharmacokinetics of PEG-IFN α-2b require that this drug be dosed depending on body weight. On the other hand, with PEG-IFN α-2a, a single dose of 180 micrograms (mcg)/week is all that is needed for the vast majority of patients (“one size fits all”). Given these differences, an understanding of the rationale and the limits of WBD is essential.

What is pegylation?
Pegylation refers to the attachment of a molecule of polyethylene glycol (PEG) to a large protein such as IFN. The PEG molecule shields IFN from enzymatic degradation and lowers its clearance from the body. This increases the time that IFN resides in the systemic circulation and may improve its distribution as well as help target IFN to its site of action in the liver.

The primary advantage of PEG-IFN over standard IFN therapy is that it can be administered only once rather than three times a week. Standard IFN leads to significant side effects related to the rise and fall in serum drug concentrations every 24 to 48 hours. Control of viral replication with standard IFN is also poor due to the fairly rapid fall-off in serum drug levels below “therapeutic” levels.

The PEG moieties of the current two PEG-IFNs differ significantly in size and shape, and this results in important differences in pharmacodynamics. The PEG moiety of PEG-IFN α-2b is a linear molecule that is 12 kilodaltons (kDa) in molecular weight (MW), whereas the PEG moiety of PEG-IFN α-2a is a larger, branched molecule of 40 kDa MW.

The different molecular structures of these agents directly account for differences in their pharmacokinetics. In fact, the linear 12-kDa PEG moiety of PEG-IFN α-2b appears to dissociate from IFN relatively soon after administration and this likely explains why its activity is fairly short in duration, about three to four days. In contrast, the 40-kDa PEG moiety of PEG-IFN α-2b is much longer, bulkier, and branched, which permits PEG-IFN α-2a to last up to five to seven days before it is broken down by the body’s immune system.

Nevertheless, both PEG-IFNs remain in the body considerably longer than the standard IFNs previously used in HCV therapy.

Metabolic parameters of PEG-IFN α-2a
In terms of key drug metabolic parameters, the maximal serum concentration of PEG-IFN α-2a is reached 72 to 96 hours after a subcutaneous injection and remains detectable for up to 168 hours. The mean terminal half-life is 80 hours, around 16 times greater than that of standard IFN α-2a. Due to the size of the 40-kDa PEG moiety, PEG-IFN α-2a is only minimally cleared by the kidneys, and instead it is broken down primarily in the liver. Since PEG-IFN α-2a is cleared relatively slowly, blood concentrations remain relatively stable throughout the week after the drug is administered.

Metabolic parameters of PEG-IFN α-2b
In contrast, the maximal serum concentra-
tions of PEG-IFN alfa-2b are achieved fairly quickly (about 20 hours) after a subcutaneous injection, and last for 48 to 72 hours. Close to 30 percent of this product is eliminated via the kidneys, and the rest is broken down elsewhere in the body. The PEG molecule is cleared via both the liver and the kidneys. With weekly doses of PEG-IFN alfa-2b, there is a 6-fold difference between peak and trough serum concentrations. This variability is much better with PEG-IFN alfa-2a (only 2-fold difference) due to the fairly steady serum concentrations achieved after multiple doses.

**Relevance of WBD with PEG-IFN**

Although both PEG-IFNs are administered once weekly, due to the specific pharmacokinetic profile of PEG-IFN alfa-2b, it must be dosed dependent on the patient’s body weight (1.0 to 1.5 mcg per kg body weight per week). On the other hand, the weekly dose of PEG-IFN alfa-2a is fixed (usually 180 mcg per week).

The main reason for this difference in dosing is the volume of distribution (Vd), a key pharmacologic parameter. The small 12-kDa PEG-IFN alfa-2b molecule is widely dispersed throughout the body, which leads to a relatively high Vd of 20 liters. Because of this large Vd, serum concentrations of PEG-IFN alfa-2b may be affected by the patient’s size, body weight, or lean/fat body mass ratio. Body weight has been shown to have a small but statistically significant effect on the clearance and activity of PEG-IFN alfa-2b, and thus body weight must be taken into account with its dosing.

As the size of the PEG molecule increases, the Vd diminishes. This is one advantage with the 40-kDa PEG-IFN alfa-2a, since its Vd is only 8 liters, which closely approximates that of normal blood volume (about 5 liters in most adults). In addition, its distribution is restricted primarily to the liver, where it is also broken down.

Thus, differences in the Vd and clearance of PEG-IFN alfa-2a among various patients are only minimally explained by differences in body weight. In fact, studies have shown that body weight explains only 1 percent of the variability in the clearance and activity of PEG-IFN alfa-2a. Consequently, a fixed-dose rather than WBD of PEG-IFN alfa-2a is recommended.

When either PEG-IFN alfa-2a or alfa-2b is used alone (as monotherapy) to treat chronic HCV infection, higher SVRs (20 percent and 13 percent higher, respectively) are achieved than with standard IFN monotherapy. Fortunately, side effects are neither more frequent nor more severe with the PEG-IFNs than the standard IFN formulations, although neutropenia appears to be more common, especially with PEG-IFN alfa-2a.

**WBD of ribavirin**

Ribavirin (RBV) is a nucleoside analogue that works best when administered in combination with IFN by augmenting the immunologic response to HCV and preventing a relapse after treatment is stopped. When given alone, RBV normalizes liver enzymes but it has no significant antiviral effect.

Since RBV has a small MW, RBV has a large Vd and serum drug concentrations are affected by body weight (as discussed earlier with PEG-IFN alfa-2b). The most serious side effect related to RBV is hemolysis, and thus WBD must be used with RBV to avoid major toxicity in smaller patients.

Furthermore, RBV cannot be used in patients who are already anemic, those at risk for heart attack, or in those with severe hepatic failure or renal dysfunction.

In general, RBV has not been dosed on a milligram (mg) per kg basis. Instead, patients receiving less than 75 kg are administered 1.000 mg per day, whereas all those weighing over 75 kg should receive 1,200 mg a day. As a safety measure, this broad cut-off point has been used in most previous studies and may be a good “ball-park” figure for most patients.

However, more recent studies suggest that WBD (on a mg/kg basis) may increase the efficacy of RBV in combination with PEG-IFN alfa-2b, although the safety of this dosing has yet to be established, especially in heavier patients. This is one of the objectives of the WIN-R trial currently in progress.

**Implications of WBD in current clinical trials**

Three recent large, multinational trials addressed the safety and efficacy of PEG-IFN and RBV in combination, although none of them specifically looked at WBD prospectively. The three trials were as follows:

1. Manns et al studied PEG-IFN alfa-2b plus RBV versus standard IFN alfa-2b and RBV; WBD analysis was done retrospectively as noted below.

2. Fried et al compared PEG-IFN alfa-2a and RBV versus PEG-IFN alfa-2a monotherapy, and standard IFN–RBV therapy.

3. Hadziyannis et al assessed outcomes with PEG-IFN alfa-2a and varying doses of RBV for different treatment durations.

In the trial by Manns et al, 1,530 patients were randomized to receive one of three treatments: 1) standard IFN 3 million units three times per week, plus RBV 1,000 to 1,200 mg/day, both for 48 weeks; 2) PEG-IFN alfa-2b 1.5 mcg/kg per week for four weeks, followed by 0.5 mcg/kg per week for 44 weeks, plus RBV 1,000 to 1,200 mg/day for all 48 weeks; or 3) PEG-IFN alfa-2b 1.5 mcg/kg week, plus RBV 800 mg/day, both for 48 weeks.

The overall SVRs were 47 percent, 47 percent, and 54 percent, respectively. Patients with genotype 1 (GT1) had SVRs of 33 percent, 34 percent, and 42 percent, respectively whereas those with non-1 GTs had SVRs of 79 percent, 80 percent, and 82 percent, respectively.

The high-dose PEG-IFN and RBV combination was significantly better than the other treatment arms of the study for GT1 patients, but not so for the other arms with non-GT1 patients.

Further analysis showed that higher doses of both PEG-IFN alfa-2b and RBV led to a higher SVR. In the high-dose PEG-IFN alfa-2b group, SVR increased as the RBV doses rose up to 13 mg/kg per day. Based on this retrospective analysis, the optimal WBD of RBV was 10.6 mg/kg per day, and the overall response for patients in the higher PEG-IFN alfa-2b group who received more than 10.6 mg/kg per day was 61 percent.

Unfortunately, all the patients in this trial who were on the consistently higher doses of PEG-IFN alfa-2b and RBV received only 800 mg/day of RBV, whereas those in the other groups received 1,000-1,200 mg/day, since the investigators were concerned that the bone marrow suppression related to PEG-IFN alfa-2b might significantly worsen the anemia related to RBV alone.

As a result, only the patients in the first group who weighed less than 75 kg actually received more than 10.6 mg/kg/d of RBV. In addition, although the side effects may be tolerated reasonably well, WBD of RBV may not always be feasible or even safe. For example, based on an optimal RBV dose of 10.6 mg/kg per day, a 160-kg
patient would need to receive almost 1,700 mg/day of RBV, which far exceeds the recommended maximum dose of 1,200 mg/day.

The WIN-R trial is currently underway to test the safety and efficacy of dosing RBV at 10.6 mg/kg per day in combination with PEG-IFN alfa-2b.

In the multicenter trial by Fried et al., 1,121 patients were randomized to receive one of three treatments: (1) PEG-IFN alfa-2a in combination with RBV; (2) PEG-IFN alfa-2a as monotherapy; or (3) standard IFN-RBV. PEG-IFN alfa-2a was dosed at 180 mcg once weekly, and RBV, when given, was dosed at 1,000 to 1,200 mg/day (based on the usual 75-kg BW cutoff). All treatment arms were for 48 weeks. The overall SVRs were 56 percent, respectively, and 29 percent, respectively.

The overall SVR in group 4 was 61 percent, and in patients with GT1 the SVR was 51 percent, the highest SVR seen until then in this population. The results for non-GT1 patients were similar among all treatment arms (82 percent, 79 percent, 73 percent, and 77 percent, respectively), which indicates that adjusting the dose or duration of RBV based on weight is not necessary for non-GT1 patients. Only six months of RBV at 800 mg/day is needed in these patients.

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References
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“The dramatic fall in deaths has been our trump card” in pushing for increased funding in the past, said Lanny Cross, Director of New York State’s ADAP, “but it’s become a harder sell.” He pointed to New Jersey where, on April 1, 2004, the list of drugs covered “went from an abundance to a very limited formulary.”

The approval of new antiretroviral drugs has been good for patients, “but not such a good thing from a price perspective,” he said. The trend has been for newer drugs to cost more, the price of older ones to increase periodically, and for a greater number of drugs to be used in salvage therapy for those who develop antiretroviral drug resistance. That all contributes to increased financial pressure.

California’s HIV programs have been among the soundest in the nation, in large part because of that state government’s supplements to federal funding. But California’s safety net is beginning to tatter. “I have health insurance and I need ADAP, too,” is one of the realities put forward at a rally earlier this year in Sacramento. It helped Californians stave off cuts to the state AIDS budget, said Michael Allerton, HIV Policy Coordinator for Kaiser Permanente, a private healthcare insurer.

One of the largest healthcare providers in California, Kaiser Permanente counts almost 10,000 people living with HIV/AIDS among its clients. Allerton is proud of the fact that 72 percent of them have undetectable viral loads. Kaiser Permanente has lost less than 1 percent of those patients over each of the last six years to all causes, including accidents and non-HIV-related conditions.

However, the financial cost to Kaiser Permanente is enormous. While only 0.16 percent of their patients have HIV, the cost to Kaiser Permanente of treating the disease is second only to that for treatment of depression.

Allerton said there is tremendous pressure from companies purchasing health insurance for their employees to reduce the cost of those policies. This is accomplished through several mechanisms, the most prevalent of which are to increase co-payments and cap what is covered. That results in poorer coverage for the patients when they most need comprehensive coverage. This has had a disproportionate impact on more costly medical conditions, including HIV.

As a result, Kaiser Permanente’s case managers, who used to counsel patients about adherence, increasingly are devoting time to issues of caps and are working with patients to qualify them for ADAP and other programs when they reach the limits set by their insurance policies.

Craig Thompson, Executive Director of AIDS Project Los Angeles, reinforced that concern. He said money is being taken out of case management to cover shortfalls in other areas, which makes it even more difficult for people living with HIV/AIDS to stitch together access to the services they need.

As Patrick Clay, a Kansas City, Missouri, pharmacologist (and IAPAC member) reminded summit participants, “it is not just about getting [patients] on therapy that we must strive to do… it is getting them and maintaining them engaged in primary care.”

Clay pointed to economic statistics to bolster his case for comprehensive HIV care across a continuum (Figure 1). He cited decreased costs in millions of US dollars due to shorter stays for fewer emergency room visits, as well as fewer hospitalizations for patients receiving comprehensive HIV care compared to those patients who may have been started on antiretroviral therapy and dropped out of clinical care. “Engagement and continuation of engagement in primary care is paramount to the success of antiretroviral therapy,” Clay explained.

And so, it would seem that as people living with HIV attempt to access the continuum of care and treatment they require, astride increasing financial constraints, greater inefficiency is also being bred into the overall healthcare system.

“As the patients do not go away,” said William E. Arnold, Executive Director of the ADAP Working Group. “If the trends continue, a whole bunch of people are not going to be treated… and they are going to crash into other parts of the healthcare system.”

A coalition effort has been successful in getting most pharmaceutical companies to agree to price freezes for ADAP. This is in part due to the argument that ADAP “is unique in that it is not a whole system,” and so the cost of the drugs is not balanced by benefits such as reduced hospitalization, said Cross. He thus does not see this as a useful model or argument for gaining price freezes in other parts of the healthcare system.

Colorado physician (and IAPAC member) Benjamin Young views the price freezes for ADAP as an acknowledgement by the pharmaceutical industry that prices are too high. He called industry access programs “only a band-aid” on the greater problem of price. In what was slated on the summit’s agenda as a “call to action,” Young urged care provider groups and advocates to redouble efforts in working with industry, government, and other stakeholders to rise to the ethical imperative of ensuring appropriate care for all people living with HIV/AIDS.

IAPAC has committed to continue dialogue with multiple stakeholders represented at the summit. This is good, said Young, who believes that physicians should take a firm stance on behalf of their patients’ interests. “Doctors have to be more involved… they have the moral obligation to become involved.” Young urged in his closing remarks, “silence is complacency, silence is an acquiescence of the status quo, silence is not acceptable.”

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Figure 1. Rationale for a continuum of HIV care

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Colette Simon

Since June 2002, the IAPAC Monthly has featured members of the International Association of Physicians in AIDS Care (IAPAC) who are asked to bare their souls by answering a series of questions similar in nature to those asked in the famous Proust Questionnaire.

This month, IAPAC Monthly is proud to feature Colette Simon, Medical Director of the Limestone Correctional Center in Madison, Alabama.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
It is a translation from French: “If you cannot be a star in the sky, be a lamp at home.”

What activities, avocations, or hobbies interest you?
Ballroom dancing, singing, and modeling.

If you could live anywhere in the world, where would it be?
I need to explore the world to really answer this question. However, of all the cities I have visited (Paris included), my favorite is Chicago. Of the islands I have visited, Aruba is my favorite. Still, I love living in Alabama.

Who are your mentors or real life heroes?
My father, Joseph Simon, who is a retired pharmacist. His love for science and sense of discipline were inspiring.

With what historical figure do you most identify?
Because of my constant attraction to the “needy,” St. Katherine Drexel, who was called Apostle to the Oppressed, and Mother Teresa are the two figures with whom I could identify. Their stories are so inspiring, and they both lived in the 20th century.

Who are your favorite authors, painters, and/or composers?
My favorite composer is Andrew Lloyd Webber, and I like the following painters: Francois Ledan, Peter Max, and Thomas Kinkade.

If you could have chosen to live during any time period in human history, which would it be?
My favorite movie is “Gone with the Wind.” I would not mind living at that time, but I have to confess that [right] between the 20th and the 21st centuries is right where I should be.

If you did not have the option of becoming a physician, what would you have likely become, given the opportunity?
An entertainer — either a singer or a dancer.

In your opinion, what are the greatest achievements and failures of humanity?
Achievements: Advances in communication (eg, cell phones, fax, e-mail); advances in transportation (eg, airplanes, space shuttles); and discoveries in genetics (eg, mapping the human genome, associating gene defects with specific disease processes). Failures: How the same achievements, inventions, or creations can be used against us. Loss of privacy with cell phones, e-mail, etc. Use of airplanes to destroy wealth and lives. Use of genetic discoveries to spread infection or to poison or to clone and God knows what else.

What is your prediction as to the future of our planet one full decade from present day?
Loss of traditional values (eg, integrity, respect for self and for others), loss of privacy and dignity, and a technological life with little room for the human touch.
The terrorist cell apparently planned to obtain contaminated blood from some Palestinian hospitals but they had not passed the preliminary stage in their preparations.

From an April 13, 2004, Agence France-Presse report entitled, “HIV Bomb Plot Foiled.” According to the spokesperson from Israel’s Shin Beth security service, Palestinian extremists attempted to carry out a suicide attack using a bomb laced with HIV-infected blood during the Passover holiday. Militants had allegedly been planning to dispatch a suicide bomber from the northern West Bank town of Qalqilya to Tel Aviv to carry out the attack. The plot was exposed after the arrest of a member of the Al-Aqsa Martyrs Brigades, a radical offshoot of Palestinian leader Yasser Arafat’s Fatah movement. Israeli security services have been on a high state of alert for fear that militants, who have vowed to avenge the Israeli assassination of Hamas founder Sheikh Ahmed Yassin, might attempt a spectacular attack.

We are exceedingly concerned about it.

Sherry McKibben, Executive Director of HIV Edmonton, quoted in an April 12, 2004, Edmonton Sun article about the Canadian city’s soaring rates of sexually transmitted infections (STIs). According to regional health officials, heterosexuals who regularly engage in casual sex are hampering efforts to trace partners in the region’s largest syphilis outbreak since the 1980s. Many of those testing positive for syphilis cannot identify their partners, leading those unknowingly infected to continue spreading the disease. In addition to syphilis, gonorrhea rates have almost doubled from 260 in 1999 to 507 in 2003. And, although 2003 statistics are incomplete, chlamydia cases, which reached 2,326 in 2002, are also expected to show increases. The number of HIV cases in Edmonton dropped slightly from 92 in 2001 to 83 in 2002, but public health experts predict that reporting delays—including fallout from the syphilis outbreak—could change that trend.

It must be reported timely and faithfully. And anyone who intends to hide the epidemic should take responsibility and will be severely punished.

Chinese Health Minister and Vice Premier Wu Yi in an April 7, 2004, speech delivered at an HIV/AIDS conference in Beijing. Wu stated a pressing need for a nationwide effort to combat the rapid spread of HIV in China. Her comments, which mark the first time a Chinese leader has threatened punishment for covering up HIV prevalence statistics, appear to be based on China’s experience with the SARS epidemic, in which an early reporting cover-up contributed to the disease spreading to more than 30 countries and causing almost 800 deaths worldwide.
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