The elephant from the other side of silence

(or HIV news from four compass points)
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Mark Mascolini

Four years after Durban’s XIII International AIDS Conference shone a white-hot light on untreated millions, Bangkok made that treatment a full-fledged part of the program. In doing what an international conference should do—review studies from an international base—the XV International AIDS Conference offered an unrivaled opportunity to compare treatment trends and setbacks in lands awash in antiretrovirals and in countries still taking their first sip.
he International Association of Physicians in AIDS Care (IAPAC) is establishing a Center of Excellence in Sharpeville, South Africa, which, in addition to offering care and support to HIV-positive citizens of the township, will serve as a medical education hub for physicians and allied healthcare professionals throughout southern Africa.

The site of an infamous massacre that was a turning point in the fight to end apartheid, and currently a deeply impoverished township suffering high incidence of HIV/AIDS, Sharpeville is a suitable location, both for symbolic and practical reasons, for IAPAC to begin its care provision effort. We have obtained an abandoned hospital complex to serve as the physical location for the Center of Excellence, and we are raising funds to begin rehabilitating the buildings and covering other expenses.

Helping in IAPAC’s effort is Melissa Fitzgerald, an actress on NBC’s political drama “The West Wing” as well as an individual who is dedicated to humanitarian outreach. As a guest of IAPAC’s African Regional Office (IAPAC-AFRO) earlier this summer, Melissa visited the future site of our Center of Excellence and spent time getting to know IAPAC staff as well as members of the Sharpeville community.

The pictures accompanying this month’s Report from the President (see page 317) represent a visual record of Melissa’s trip. They offer a glimpse of both the challenges and the resilient hope that is everywhere evident in Sharpeville. I hope to report additional good news in the near future. In the meantime, I welcome your support!

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

(Clockwise from top) Actress Melissa Fitzgerald, IAPAC staff members, and a Sharpeville township council member inside the future site of IAPAC’s Center of Excellence; Fitzgerald visits a children’s center; and she listens to a Sharpeville resident’s description of the impact of HIV/AIDS on the impoverished township.

Photo credit: Kristin T.M. Burns
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HIV meetings big and small stick “international” in their titles with all the premeditation of callow youth offering virgin skin to bad tattooists. Conclaves accommodated in modest hotel rooms and populated by personages who call Western Europe and North America home have become “international,” as have lesser assemblies.

For all its excess and oft-fuzzy focus, the biennial International AIDS Conference at least lives up to its name. This year’s Bangkok extravaganza—six steamy days’ worth of plenaries, parades, PowerPoints, pyrotechnics, posters, protests, and Global Village goings-on—gathered some 20,000 people with HIV (and those who treat, count, counsel, govern, or exploit them) from all populated continents and many depopulated corners of the world.

The 2004 gathering, fulfilling an International AIDS Society (IAS) promise to host these marathons alternately in countries most beset by HIV, raised prickly questions about the conference’s future. Noted AIDS scribes fussed in print over the program’s fleeting heed to high science. Their remonstrations did not lack merit. Time was when one waited in opening and closing ceremonies for the token
activist. In Bangkok one waited for the token scientist. The confabulatory kickoff featured two lone epidemiologists aswim in a sea of politicians, beauty queens, and the token activist (tacked on at the end). The closing ceremony featured none—or at least none who spoke about AIDS science.

Attending the clinical sessions in rooms separated from neighbors by flimsy portable walls, one often felt a whole other conference might be going on next door—something with a raucous disregard for Robert’s Rules of Order. Clinical speakers sometimes had to wait for the next-door noise to wane. One longed at times for those cozy “international” causeries of 200 genteel genotypers.

But it is not true, as some aver, that Bangkok was a scientific bust. After all, the abstract book lists more than 6,000 reports on basic science, clinical research, and epidemiology. The attendee who could not find something to inform his practice or rejigger her research in all that spent too much time walking through wats in downtown Bangkok. The reporter stuck for headlines spent too much time tracking Richard Gere.

HIV science does not advance in increments timed to convenience International AIDS Conference goers. Of the 15 international round-ups so far, three at most (20 percent) have marked milestones in the epidemic. (See note 3 for nominations.) Only bad gamblers go to these gatherings expecting a new gestalt.

What one should expect at the International AIDS Conference is a big dollop of puffery and huffery. This is the conference where HIV becomes HIV/AIDS, the epidemic becomes a pandemic, and attendees become delegates. This is the conference that tries to embrace every party to the epidemic and inevitably ends up spawning polemics, pouts, and finger pointing.

But the XV International AIDS Conference, like every big conference,
had its differences. Just as Bangkok, like every big city, has its own problems. Other cities have murderous traffic jams (and Bangkok has them too). Other cities have shimmering skyscrapers with vagrants at their doorstep (as does Bangkok). And other cities have lung-fouling smog and fetid waterways (like those found in Bangkok). But only Bangkok has

Elephants

Elephants downtown. Getting their feet caught in drains, playing football, thrilling tourists, and stampeding merchant stalls. The problem, apparently, can be traced to a steep falloff in logging (wherein most elephants found their employ) and Thailand’s economic downturn. Those forces led many mahouts (handlers) and their shuffling brutes into cities to earn their keep keeping tourists enthralled.

One stately pack of pachyderms appeared at the first-night fest of this International AIDS Conference, delighting all. Only in the following day’s The Nation did attendees learn that one of the featured performers, perhaps named Sud Lor (“Absolute Handsome”), figured in the off-site death of a construction worker. The Bangkok daily’s first page featured a photo of police collecting interdigital earthen samples from Sud Lor above a four-column headline: “Killer beast linked to conference.” The worker’s brother alleged that Sud Lor grasped the luckless man with his trunk and smashed him to the ground, but the elephant’s mahout dismissed the claim, lying down “before the beast and sarcastically asking it to gore him.” Instead, the 19-year-old behemoth knelt down and cried.

That’s the way with elephants. Whether they’re killing or contrite, they’re hard to ignore. Three elephants, indeed, march with trumpeting trunks across the conference logo. (Whether they replaced a depiction of two adult tuskers copulating while a calf looked on “with mild interest” could not be confirmed.) But making oneself painfully obvious has its rewards. For almost two decades, the world beyond antiretrovirals was the elephant in the living room of HIV science. International AIDS Conferences started paying attention to global AIDS, at least in their slogans, with the first non-West meeting in Yokohama, which sought to bring HIV workers “Together for the Future” in 1994.

Ten years later—and four years after the Durban congress shone a white-hot light on untreated millions—Bangkok made that treatment a full-fledged part of the program. Among the clinical slide sessions this reporter attended, 21 of 62 talks (34 percent) featured studies in poor or developing countries. And none of these sessions focused solely on what one might call a developing country issue, such as mother-to-child transmission or generic antiretrovirals. In doing what an international conference should do—review studies from an international base—the International AIDS Conference stands a slimmer chance of commanding the interest of Western clinicians or reporters. But a conference built on this plan offers an unrivaled opportunity to size up two issues side by side, North versus South or West versus East:

- Over the years, progression to AIDS in treated people worsened.
- Over the years, the six-month virologic response to first-line therapy improved.
- Over the years, treatment’s side effects.

These issues form the gist of this article. An intermezzo between these stanzas will look at a problem full blown in lands of antiretroviral plenty but in first flower elsewhere—treatment’s side effects.

RESHAPING THE EPIDEMIC

(North/West)

Anyone who tells you that the XV International AIDS Conference produced no important clinical news missed a talk by Matthias Egger (University of Bern, Switzerland) [abstract TuOrC1157]. In a little-noted but surprising report from the ART Cohort Collaboration, Egger offered evidence that highly active antiretroviral therapy (HAART) has not been performing as advertised. This massive amalgam of data from 12 prospective cohorts of people starting antiretrovirals in Europe and America since 1995 reached two seemingly contradictory conclusions:

- Over the years, progression to AIDS in treated people worsened.
- Over the years, six-month virologic response to first-line therapy improved.

The study did not, however, pin down the reasons for this faster track to AIDS or death

Egger’s analysis, poised for a virtual thumb-through at www.art-cohort-collaboration.org, involved 12,379 people with an average age of 37.5 years. Nearly one third were female, and 23 percent had AIDS when they started therapy. Their median year for starting HAART was 1999, a date reflected in the key component of the first regimen: 68 percent traded their naive status for a protease inhibitor (PI) and 26 percent for a nonnucleoside reverse transcriptase inhibitor (NNRTI).

### Table 1. Probability of AIDS or death in ART Cohort Collaboration

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<th>&lt;5 log baseline</th>
<th>≥5 log baseline</th>
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<td>9.3</td>
<td>7.7</td>
<td>7.9</td>
<td>6.5</td>
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</table>

Everyone in this analysis was younger than 50 years and had no history of injecting drug use.

Source: Matthias Egger, abstract TuOrC1157.

The ART Cohort Collaboration counted 1,885 new AIDS diagnoses and 1,005 deaths through 61,798 person-years of follow-up. As in earlier analyses, they figured progression risks on the basis of:

- Age 50 or above versus below 50
- Risk group
- CDC disease stage
- CD4 stratum
- Viral load at or above 5 logs versus below 5 logs

In this new study, however, Egger and colleagues figured progression risk one, two, three, four, and five years after therapy began. Looking at people younger than 50, with a pretreatment viral load below 100,000 copies/mL, and without a history of injecting drug use (IDU), they found only a 1.2 percent five-year difference in progression for people starting therapy below or above 350 cells/mm³ (Table 1). Egger cautioned, though, that this finding cannot be read with the confidence of randomized trial results. Still, the number corroborates and lengths similar short-term results.

A logistic regression model controlling for pretreatment prognostic variables logged a year-to-year climb in probability of notching an undetectable viral load after six months of therapy. Compared with aviremia rates in 1995-1996, the chance of having a six-month undetectable load was 2.1 times higher in 1997, 3.3 times in 1999, 3.5 times in 2000, and 4.0 times in 2001-2002. Those odds ratios proved better in gay men (2.3 in 1997, 3.8 in 1999, 4.7 in 2000, 6.5 in 2001-2002) than in IDUs (1.4 in 1997, 1.8 in 1999, 2.2 in 2000, 2.2 in 2001-2002).

Then came the surprise: The risk of AIDS or death, but not of death alone, rose in the most recent years of the analysis. Compared with the reference year 1998 (1.0), a new AIDS diagnosis or death proved 1.11 times more likely in 1995-1996 and 1.17 times in 1997. After 1998 progression risk resumed a slow but inexorable ascent, from 1.06 in 1999, to 1.13 in 2000, 1.20 in 2001, and 1.33 in 2002-2003. In other words, in a Cox regression model controlling for prognosis predictors at baseline, post-treatment AIDS has become more likely in more recent years.

Why? One possibility, Egger offered, is that the uptrend is a misleading artifact of more thorough scrutiny for AIDS end-points in this collaborative effort. But the trend could just as easily be fact as artifact. Egger posed the possibility that European and American cohorts are changing to include more recent immigrants or others who seek treatment late in their disease course, when the risk of AIDS is higher. And perhaps years of hearing about HAART’s restorative prowess have made clinicians lax in starting standard prophylaxes.

Such hypotheses are not all airy thinness, as another result of this research shows. The median pretreatment viral load in the ART cohorts has stuck stubbornly at 5.0 logs since 2000, an uptick from the median 4.9 logs from 1997 through 1999. As earlier work by this team demonstrates, starting treatment with a viral load above 5 logs (100,000 copies/mL) heightens the risk of disease progression.

And while the median starting load has dug in at 5 logs, the median starting CD4 count has dropped—from 261 cells/mm³ in 1997, to 237 cells/mm³ in 1998, and to 200 cells/mm³ or lower from 2000 to 2003. Those crumbling starting numbers may well reflect the immigration of people with more advanced disease or failure to seek treatment by the growing proportion of poor or rural African Americans infected with HIV. Several conference studies reviewed later in this section detail the rates and consequences of late HIV diagnosis in Europe and the United States (see “Late”). The problem is entrenched, if not intractable.

A separate analysis of ART Cohort Collaboration dossiers by Caroline Sabin (Royal Free and University College Medical School, London) confirmed that starting antiretrovirals with a six-digit viral load heightens the risk of progression to AIDS [abstract TuPeB4532]. At the same time, unlike several other studies, Sabin’s exegesis discerned a clear jump in progression risk when starting treatment between 200 and 349 cells/mm³ rather than 350 cells/mm³ or more.

Sabin logged all first new AIDS diagnoses during the first three years of treatment in 22,217 people. Over a median 2.5 years of follow-up, she counted 2,142 AIDS “events” for an incidence of 49 per 1,000 person-years. Age, type of regimen taken, and the year therapy began did not influence progression to AIDS, but pre-treatment CD4 count and viral load, time since starting treatment, an earlier AIDS diagnosis, and injecting drug use did:

- Time since starting therapy: Relative rate (RR) 0.41 per year, \( P = 0.0001 \)
- Injecting drug user: RR 1.22 versus homosexual, \( P = 0.01 \)
- Previous AIDS: RR 2.95, \( P = 0.0001 \)
- Baseline load above 100,000 copies/mL: RR 1.32, \( P = 0.0001 \)
- Baseline CD4 count below 50 cells/mm³: RR 7.50 versus \( \geq 350 \) cells/mm³, \( P = 0.0001 \)
- Baseline CD4 count 50 to 199 cells/mm³: RR 4.04 versus \( \geq 350 \) cells/mm³, \( P = 0.0001 \)
- Baseline CD4 count 200 to 349 cells/mm³: RR 1.79 versus \( \geq 350 \) cells/mm³, \( P = 0.0001 \)

**Infants**

Early response to antiretrovirals proved even more troubling in a small study of 155 infants in the United Kingdom or Ireland starting treatment before their first birthday [abstract TuOrB1188]. Katya Doerholt (MRC Clinical Trials Unit, London) reported that only 84 (54 percent) gleaned a viral load below 400 copies/mL 12 months into their treatment course.

Most HIV-infected children in the 18-center study had mothers who didn’t know their HIV status at delivery. About three quarters of the children were black Africans. Their CD4 response to early therapy offered more grounds for optimism, rising from a median of 22 percent when antiretrovirals began to 32 percent after six months.

Doerholt attributed HIV disease progression before treatment to poor clinic attendance and poor adherence with prophylaxis for *Pneumocystis pneumonia*. She blamed poor antiretroviral adherence and resistance for the worrisome virologic response rate. Doerholt called for greater collaboration among current infant cohorts to get a better grasp on response rates and reasons.
But projected mortality for both men and women with HIV outran that of the general population. And only a minority can expect to live as long as people with diabetes.

These researchers figured standardized mortality ratios among HIV-infected people one year after starting their first antiretrovirals then compared those rates with ratios in an age- and gender-matched sampling of the general population. The HIV group had a median age of 37 years (interquartile range [IQR] 32 to 45 years), 79 percent were men, and 56 percent gay. They began treatment with a median CD4 count of 250 cells/mm³ and a median load of 100,000 copies/mL. Follow-up after antiretrovirals began averaged 3.5 years.

Van Sighem recorded 101 deaths through 11,373 person-years of follow-up to yield a death rate of 0.89 (95 percent confidence interval [CI] 0.72 to 1.08). The risk of death fell as CD4 counts rose after 24 weeks of therapy ($P < 0.001$). Only two factors independently predicted a slicker slope to death at the following hazard ratios [HR]:

- Lower log CD4 count after 24 weeks: HR 0.47
- RNA above versus below 5 logs at 24 weeks: HR 0.31

Compared with the general population, men with HIV had a higher death rate through about 60 years of age. Mortality among HIV-infected women didn’t balance with women in the general population until about 70 years of age. Among HIV-infected people judged successful treatment responders—who those who reached a CD4 count above 600 cells/mm³—the death rate matched that of a general population group with diabetes. Only 16 percent of the ATHENA cohort had a 24-week count above 600 cells/mm³, but that’s an alpine standard for a group starting therapy at 250 cells/mm³. Still, if one accepts this analysis at face value, it suggests that HIV infection has not become just another chronic disease for antiretroviral-treated people.

**Late**

As researchers plumb reasons for doggedly high mortality among people taking purportedly life-saving antiretrovirals, they routinely finger late diagnosis of HIV infection as a prime culprit. Several studies at the Bangkok caucus asked why people show up late for HIV tests and what happens when they do.

A five-city study by Scott Kellerman (US Centers for Disease Control and Prevention [CDC, Atlanta]) documented an astonishingly high rate of late HIV testing—58 percent—in people 13 years old or older with an AIDS diagnosis reported in 1999 or 2000 [abstract TuOrC1161]. Among 2,063 people diagnosed in Boston, Chicago, Hartford, Los Angeles, and San Francisco, 1,175 met the study definition of late testing—an HIV assay within six months of the AIDS diagnosis.

More than half of the late testers, 56 percent, were younger than 40 years old, and 46 percent were men who had sex with men. A multivariate model nosing out the risk of late testing calculated a 1.4 times higher risk among blacks than whites (95 percent CI 1.1 to 1.9) and a 1.7 times higher risk among Hispanics than non-Hispanic whites (95 percent CI 1.4 to 2.2). Not having health insurance did not raise the risk of late testing.

In another multivariate analysis people from 40 to 49 years old proved 30 percent more likely to go without antiretrovirals before their AIDS diagnosis when compared with people 30 to 39 years old. People aged 50 and older were 20 percent more likely to do without treatment before their AIDS diagnosis. Compared with whites, blacks had a 50 percent higher chance of getting AIDS before getting antiretrovirals, and Hispanics had a 30 percent higher chance.

Kellerman cautioned that these treatment numbers may be inaccurate because they come from chart reviews, not from interviews with physicians or the infected people themselves. The sorry statistics in this study may not apply to other places in the United States, he added. That means they could be better or worse elsewhere.

A single-center study in the southeastern United States, where HIV prevalence has risen disproportionately in the past few years, confirmed the CDC’s finding of rampant late diagnosis [abstract MoPeC3547]. C.L. Gay (University of North Carolina, Chapel Hill) found that 79 percent of 348 people making their first HIV visit at this clinic from 2000 through 2003 met US criteria for starting antiretrovirals (CD4 count below 350 cells/mm³, viral load above 55,000 copies/mL, or an AIDS-defining disease).

A multivariate analysis that considered gender, age, race, insurance, distance to the clinic, rural residence, substance abuse, and depression singled out male gender and rural residence as the only independent predictors of late care. Men had a 2.5 times higher risk of coming in late than women (95 percent CI 1.2 to 5.0, $P = 0.01$), and rural residents (those living in communities of fewer than 50,000 people) had a 2.2 times higher risk (95 percent CI 1.0 to 5.1, $P = 0.04$). Notably, latecomers proved no more likely to be black than white at this clinic.

If the promise of potent therapy has not brought flocks to US HIV testing centers, it hasn’t done much better in Belgium, Britain, or France. Surveying the Belgian national HIV diagnosis database from 1992 through 2002, André Sasse (Scientific Institute of Public Health, Brussels) [abstract MoPeC3630] saw CD4 numbers reflecting those reported by the ART Cohort Collaboration (see “AIDS or death” above): The average CD4 count at HIV diagnosis drifted from 394 cells/mm³ in 1992 to 354 cells/mm³ in 2002 ($P < 0.05$), though the later number still stood 150 cells/mm³ above the diagnostic average in the collaborative analysis.

The Belgian team did confirm one conjecture of the collaborative group’s Matthias Egger—a lower CD4 count at diagnosis among recent immigrants (337 cells/mm³) than among native Belgians (422 cells/mm³, $P < 0.01$). CD4 counts also proved lower at diagnosis among women than men (357 versus 372 cells/mm³, $P < 0.01$). And lower counts at diagnosis correlated with older age ($P < 0.01$). But in a model adjusted for age, gender, and nationality, the drop in CD4 tallies at diagnosis over the 10-year span lacked statistical significance.

Caroline Sabin reported that 100 of 677 people (15 percent) diagnosed with HIV at London’s Royal Free Hospital from 1996 through 2002 had a first CD4 count below 50 cells/mm³ [abstract MoPeB3356]. The larger share of those with a late diagnosis, 57 percent, had at least one AIDS condition at their first visit, compared with 7 percent of people diagnosed with a CD4 count above 50 cells/mm³. Multivariate manipulations picked out three independent predictors of late diagnosis:

- Older age: odds ratio (OR) 1.04 per year older, $P = 0.0005$
Mary-Krause (Inserm EMI 0214, Paris) 

Hospital Database on HIV by Murielle experience an undetectable viral load."

likely to experience a reasonable response long enough to start [antiretrovirals] . . . are concluded. But "those who do survive and [their] prognosis may be poor," Sabin (particularly during the first few months), major demands on hospital resources sent with multiple AIDS events, place more new AIDS illnesses during follow-up. Twenty-six “late presenters” had one or pared with the earlier-diagnosis group. 

response in the late-diagnosis group com— up. But Sabin noted an “attenuated” CD4 viral rebound through 2.7 years of follow—

400 copies/mL and about 14 percent had a percent had at least one viral load below 300 copies/mL. Among the 89 who did start therapy, 87 died shortly after their HIV diagnosis. 

begin antiretrovirals, nine because they sis at the Royal Free clinic. 

Race was not a factor in late HIV diagno— at the Royal Free clinic. 

Eleven of the “late presenters” did not begin antiretrovirals, nine because they died shortly after their HIV diagnosis. Among the 89 who did start therapy, 87 percent had at least one viral load below 400 copies/mL and about 14 percent had a viral rebound through 2.7 years of follow-up. But Sabin noted an “attenuated” CD4 response in the late-diagnosis group compared with the earlier-diagnosis group. Twenty-six “late presenters” had one or more new AIDS illnesses during follow-up. 

“Those diagnosed late commonly pre— with multiple AIDS events, place major demands on hospital resources (particularly during the first few months), and [their] prognosis may be poor,” Sabin concluded. But “those who do survive long enough to start [antiretrovirals] . . . are likely to experience a reasonable response to treatment, and most will ultimately experience an undetectable viral load.”

A much larger analysis of the French Hospital Database on HIV by Murielle Mary-Krause (Inserm EMI 0214, Paris) again linked later diagnosis and treatment with older age and getting HIV in some way besides gay sex [abstract ThPeB7138]. But this analysis linked birth in sub-Saharan Africa or residence outside France with tardy diagnosis. The French team also found a small but significant surge in late treatment in more recent years. Defining delayed access to care as starting therapy with AIDS or a CD4 count below 200 cells/mm³, Mary-Krause figured that the proportion who sought care late crept from 32.5 percent in 1997-1999 to 34.2 percent in 2000-2002. Because the analysis embraced 22,292 people, this seemingly small spurt reached statistical significance (P = 0.013). A multivariate regression model flushed out eight independent predictors of delayed access to care (Table 2).

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People who came to care with advanced disease in French hospitals died significantly more often than those diagnosed earlier. In the first two years after entering the French hospital database, 9 percent with a late diagnosis died versus 1 percent with an earlier diagnosis. In the first six months after entering the database, late presenters had a 16 times higher risk of death (95 percent CI 11.4 to 21.6). After the first six months the late presenters had a four times higher risk of death (95 percent CI 3.3 to 4.8). 

Analysis of the far-flung CASCADE cohort, drawing on groups from Europe, Canada, and Australia, found comparable CD4 responses in people starting treatment after a late or earlier HIV diagnosis but a worse virologic response in the late group [abstract TuPeB4545]. Rodolphe Thiébaut (University of Bordeaux) charted CD4 and RNA changes in 943 people who took their first antiretrovirals as part of a potent regimen. Those who already had an AIDS disease when they started HAART had a significantly lower CD4 count than those without AIDS, 206 versus 382 cells/mm³ (P < 0.0001). But the CD4 responses to therapy were similar in the AIDS and non-AIDS groups. When Thiébaut compared people first treated nine years or later after seroconversion with people treated earlier, he found a lagging RNA response in the late group. Their viral load fell 0.67 log less per year than the earlier-treated group (P < 0.0001).

The analysis also showed that injecting drug users first treated at viral loads and CD4 counts similar to gay men had a worse short-term RNA response (-2.13 versus -2.54 logs at 1.5 months, P = 0.03) and a worse long-term CD4 response (522 versus 631 cells/mm³ at 24 months, P < 0.0001).

Alcohol

Earlier diagnosis of HIV infection depends more than a little on national commitment and planning. But once an infected person gets tested, that person and the clinician

<p>| Table 2. Who gets HAART late in the French hospital system? |
|------------------------|------------------------|------------------------|</p>
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<th>n with late care (%)</th>
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<td></td>
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<tr>
<td>Cities outside Paris</td>
<td>6,411</td>
<td>2,014 (31.4)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Paris</td>
<td>10,948</td>
<td>3,622 (33.1)</td>
<td>1.06</td>
<td></td>
</tr>
<tr>
<td>Provence, Alps, Côte d’Azur</td>
<td>3,055</td>
<td>1,002 (32.8)</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td>French Dept of America</td>
<td>1,568</td>
<td>618 (39.4)</td>
<td>1.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>La Réunion</td>
<td>310</td>
<td>113 (36.5)</td>
<td>1.30</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Multivariate logistic regression model.

IDU = injecting drug user; MSM = men who have sex with men.

Source: Murielle Mary-Krause, abstract ThPeB7138.
share the responsibility for care. The XV International AIDS Conference attracted several studies on two immediately remediable health problems that every clinician and infected person should address — drinking and smoking.

At Boston University a longitudinal study of 203 people taking antiretrovirals and 304 not on treatment tied heavy drinking to a significantly higher viral load and moderately lower CD4 count in a model that adjusted for adherence, age, gender, homelessness, race, year of study entry, HIV risk, and time since first observation [abstract MoPeB3385].

Jeffrey Samet based the analysis on two cohorts, one tracked from July 1997 through July 2001, the other from August 2001 through November 2003. The group was 41 percent black, 37 percent white, and 22 percent with other racial or ethnic origins. Four in five were men, and the median age was 41 years (range 20 to 66 years). Among people taking antiretrovirals, 60 percent did not drink, 10 percent called themselves moderate drinkers (one to 14 drinks weekly and no more than four daily for men, and one to seven drinks weekly and no more than three daily for women), and 30 percent admitted heavy drinking.

Drinking did not significantly affect viral load or CD4 count in the group not taking antiretrovirals. But in the treated group the mean viral load rose with heavier drinking, and the heaviest drinkers had a significantly higher load than did abstainers (Table 3). CD4 counts were also lower among unbridled imbiers, but not significantly so.

Samet proposed that if future work confirms the link between drinking and higher viral loads, the mechanism could be pursued by assessing:

- Alcohol’s immunologic impact in people with HIV
- Alcohol-antiretroviral interactions
- Antiretroviral levels in drinkers
- More precise measures of adherence

Pamela Dole (Greenwich House, New York) found that the simple CAGE questionnaire (see note 8) readily identifies problem drinkers with HIV infection and that drinkers suffer an array of physical and psychological problems related to HIV, ethyl alcohol, or both [abstract ThPeB7252].

This cross-sectional survey of 1,072 HIV-infected people in the United States, Taiwan, and Norway relied on the CAGE questions, interviews, and a self-administered test. The convenience sample included 341 women (32 percent), 449 Africans or African Americans, 273 whites, and 126 Asians or Pacific Islanders.

CAGE results classified 144 respondents (13.4 percent) as problem drinkers. (They answered "yes" to two or more questions.) Compared with people who didn’t have a drinking problem, those who did complained significantly more often of a long list of problems:

- Worse general physical condition ($P = 0.000$)
- Worse general psychological condition ($P = 0.000$)
- Less social support ($P = 0.002$)
- Decreased engagement with healthcare provider ($P = 0.003$)
- Took less advice from healthcare provider ($P = 0.002$)
- Less confidence in HIV medicines ($P = 0.02$)
- More body changes and distress related to HIV medicines ($P = 0.01$)
- Felt HIV was causing distress and decreased "self-efficacy" ($P = 0.03$)
- Felt less control over HIV and HIV treatment ($P = 0.03$)
- More HIV symptoms ($P = 0.04$)
- Increased severity and intensity of HIV symptoms ($P = 0.02$)
- More depressed on all standard test subscales ($P = 0.000$)

Dole concluded that the CAGE questions can be an easy way to pick out problem drinkers with HIV. She also found that drinkers were more likely to use illegal drugs and to smoke or chew tobacco.

**Tobacco**

Smoking kills. This is not news. But in the first decade of the epidemic, nobody fretted too much about smoking by people with HIV, because HIV killed much faster. That all changed circa 1995, of course, when a better mix of drugs evened the mortal odds between HIV and nicotine. And when certain antiretrovirals turned out to hoist the risk of heart disease, getting people with HIV to snuff their butts permanently assumed even greater urgency.

Smoking remains a big problem in the United States and an even bigger problem...
in Europe and Asia. In a study of 881 people with HIV, US Veterans Affairs (VA) researchers found that smoking limits not only life’s quality, but also its length [abstract MoPeB3262]. As in Pamela Dole’s just-reviewed drinking study, smokers in the VA cohort tended to be drinkers, and drinkers smokers. Comparing 182 people from three VA centers who never smoked with 699 who ever smoked, Kristina Crothers (Yale University, New Haven, Connecticut) rated 11.5 percent of non-smokers versus 22.3 percent of smokers as smokers and 22.3 percent of smokers as drinkers (P < 0.001).

The only other demographic difference between the groups was a higher rate of current or former injecting drug use among smokers (68.8 percent) than nonsmokers (37.9 percent) (P < 0.001). Crothers also spotted a trend toward higher viral loads among smokers (6.7 versus 5.6 logs, P = 0.1), disturbing numbers since about 90 percent in both groups took antiretrovirals. Women made up only about 2 percent of the cohort.

Over the relatively short four-year course of this analysis, smoking-related deaths appeared to be the legacy of lung disease more than heart disease. Smokers did not differ from nonsmokers in prevalence of coronary artery disease, congestive heart failure, cancer, esophageal candidiasis, or Pneumocystis pneumonia. Crothers traced a trend toward more bacterial pneumonia among nicotinephiles (19.3 versus 13.7 percent, P = 0.08). And weed wielders did significantly worse in measures of:

- Cough or shortness of breath (46.6 versus 30.0 percent, P = 0.001)
- Quality of life of SF-12 scale (39.0 versus 47.7 percent, P < 0.001)
- Chronic obstructive lung disease (13.5 versus 7.7 percent, P = 0.04)

These (and doubtless other) differences added up to significantly more deaths among smokers through four years of observation, at an unadjusted all-cause mortality of 4.59 versus 2.34 deaths per 100 person-years (P < 0.001). Kaplan-Meier mortality curves for the two groups diverged instantly. Four years later about 16 percent of smokers versus 10 percent of nonsmokers were dead (P = 0.02).

A multivariate Cox model determined that ever smoking raised the risk of death 2.57 times (95 percent CI 1.39 to 4.75). The other independent predictors of death were age, CD4 count, viral load, and hemoglobin. These findings may prove admonitory to smokers with HIV.

A cross-sectional study of 52 antiretroviral-treated US residents entering a lipid-lowering trial (49 of them men) estimated a 9 percent 10-year risk of cardiovascular disease [abstract WePeB5902]. David Wohl (University of North Carolina, Chapel Hill) also figured that if all 19 smokers in the group quit, the heart disease risk faded by 42 percent.

Another way smoking may bring people with HIV closer to death’s door, according to results of a case-control study in Miami, is by raising the risk of renal disease [abstract MoPeB3274]. That finding may be particularly edifying for people taking antiretrovirals that discomfit the kidneys. Maria José Miguez (University of Miami) studied 534 HIV-infected adults admitted to Jackson Memorial Hospital, finding that 58 (11 percent) came in with renal insufficiency. Kidney problems affected women (22) as much as men (36) in this largely black, Haitian, and Hispanic population.

Most of the study group—69 percent—smoked, burning through an average 15 cigarettes a day with little difference between men and women. Linear regression analysis linked smoking for more than 10 years with a seven times higher risk of renal insufficiency (P = 0.02). Unfortunately, these investigators didn’t report what other variables the model considered or whether specific antiretroviral regimens correlated with kidney disease.

Nor did the authors speculate on how smoking provokes kidney disease in people with HIV, though possible contributors are altered intrarenal hemodynamics or sympathetic activity, direct tubular damage, changes in intrarenal hormones, and oxidative stress. Studies in the general population tie smoking to a heightened risk of end-stage renal disease in men with primary kidney disease and to higher creatinine levels in older people.

In the Miami study, CD4 count and viral load did not differ between those with and without renal insufficiency. Given the high rate of smoking in this cohort, it’s not surprising that respiratory complaints accounted for 51 percent of hospital trips. But the analysis did not correlate smoking with lung disease.

### Kidneys

HIV-associated nephropathy ranked as the third leading cause of end-stage renal disease among African Americans in 1999, researchers from the University of North Carolina, Chapel Hill, observed [abstract MoPeB3249]. Charting the prevalence and incidence of renal disease in 633 HIV-infected people treated at that clinic, Prema Menezes and coworkers learned that microalbuminurea and immune suppression strongly predicted development of proteinuria.

From the baseline cohort of 633 people, 342 had follow-up urinalyses after a median of seven months (range one to 10 months). The group was about 60 percent African American and 30 percent female, with a mean age of 42 years. Just over half had a viral load below 400 copies/mL, while about one quarter had a CD4 count below 200 cells/mm³. Approximately three quarters were taking a potent antiretroviral regimen.

Defining microalbuminurea as a microalbumin to creatinine ratio greater than 30 mg/g and proteinuria as a protein to creatinine ratio greater than 300 mg/mg, Menezes found 12 percent had microalbuminurea and 12 percent had proteinuria at baseline. Among those with no renal dysfunction at baseline, the incidence of microalbuminurea measured 17 cases per 100 person-years (95 percent CI 11 to 24). Multivariate analysis linked several factors to a higher risk of prevalent microalbuminurea or proteinuria at the following prevalence odds ratios (POR) and 95 percent CIs:

| Table 3. Drinking drives up viral loads in people taking antiretrovirals* |
|-----------------------------|-----------------------------|-----------------------------|
|                             | No drinking | Moderate drinking | Heavy drinking |
| n                           | 122         | 20               | 61             |
| Mean viral load (standard error) | 2.1 logs (0.2) | 2.3 logs (0.25) | 2.4 logs¹ (0.23) |
| Mean CD4 count (standard error) | 425 (39)    | 390 (35)         | 398 (32)       |

* A linear regression model adjusted for adherence, age, gender, homelessness, race, year of study entry, HIV risk, and time since first observation. See text for drinking definitions.

1P < 0.05 versus no drinking.

Source: Jeffrey Samet, abstract MoPeB3385.
• Diabetes: POR 2.8 (1.5 to 5.1)
• <350 CD4 cells/mm³: POR 2.2 (1.5 to 3.3)
• Hypertension: POR 2.0 (1.3 to 3.1)
• Hepatitis C virus: POR 1.6 (1.0 to 2.7)
• Female gender: POR 1.5 (1.0 to 2.3)
• African-American race: POR 1.2 (0.8 to 1.9)

A low CD4 count and baseline microalbuminuria proved the strongest predictors of emergent proteinuria:

• <350 CD4 cells/mm³: POR 11.0 (1.3 to 91.1)
• Microalbuminuria at baseline: POR 5.1 (1.9 to 13.4)
• Diabetes: POR 2.3 (0.4 to 13.5)
• No antiretroviral therapy: POR 2.2 (0.5 to 9.7)
• African-American race: POR 1.3 (0.3 to 4.9)

Menezes suggested that “monitoring of renal function particularly microalbuminuria may be indicated among HIV-infected persons.”

Among PIs, indinavir (IDV) has the most tainted renal toxicity history, so HIV-NAT investigators in Bangkok tried trimming IDV doses in 200-mg increments to ease kidney rigors in people with persistent renal impairment [abstract WePeB5956]. In the short 16-week follow-up presented by Mark Boyd, the tactic seemed to be working. He pared doses of the PI in 22 men and six women taking 800, 600, or 400 mg of IDV daily. All had creatinines topping 1.4 mg/dL at least twice during three months of IDV therapy. Mean creatinine measured 1.69 mg/dL (0.28 standard deviation [SD]), and mean estimated creatinine clearance stood at 47.27 mL/min (12.16 SD). The group’s average weight lay well below Western nets at 58.0 kg (9.8 SD).

IDV troughs and peaks dipped significantly at a median of 16 weeks after the first dose reduction ($P = 0.001$), but the proportion of people with sub-50-copy viral loads climbed from 79 percent to 93 percent. Rates of grade 2 to 4 pyuria (pus in the urine) dropped, and diastolic blood pressure fell significantly ($P = 0.025$). Renal function, reflected in mean creatinine and creatinine clearance, improved but did not return to pre-IDV levels. Almost everyone had a pretreatment creatinine below 1.4 mg/dL, whereas only four of 19 men and two of four women had regained that level at the end of follow-up. Boyd and colleagues continue to track these people.

The cohort consisted mostly of women and girls (55.6 percent) with a median age of 34 years ($IQR$ 29 to 40) and a median CD4 count of 71 cells/mm³ ($IQR$ 22 to 143 cells/mm³). More than one third (38.7 percent) had World Health Organization (WHO) stage 4 disease. MSF estimated the following probabilities of 24-month survival based on six-month CD4 counts:

- >200 cells/mm³ at six months: 96.5 percent
- 50 to 200 cells/mm³ at six months: 94.3 percent
- <50 cells/mm³ at six months: 87.2 percent

The MSF team also reported outcomes for 692 people treated for up to 18 months. Just more than half were women, and half had WHO stage 4 disease when they left the ranks of the treatment naive. The baseline CD4 count stood at a desperate 58 cells/mm³ ($IQR$ 13 to 192 cells/mm³), and 99 percent started an NNRTI regimen.

At the time of this report, 525 people (75.7 percent) continued treatment, 114 (16.5 percent) had died (half in the first three months of therapy), 51 (7.4 percent) stopped returning for visits, and three (0.4 percent) quit treatment. Among people still being treated, the median CD4 count rose 163 cells/mm³ (Table 4). MSF did not report virologic or adherence data.

**Missing**

Unlike the MSF update (above), a report on free antiretroviral initiatives in four African cities—Nairobi, Kampala, Abidjan, and Dakar—did include viral load and adherence findings, and the results underline some slips in starting and running such programs smoothly [abstract ThPeB7158]. In a missing-data-equal-failure analysis, Papa Salif Sow (Universitaire de Fann, Dakar) reported that 53 percent of 207 people had a week 24 viral load below 400 copies/mL, a middling result largely attributable to missing data from one site.

The two-year-old program offers saquinavir/ritonavir (SQV/RTV, 1,600/100 mg once daily) plus zidovudine/lamivudine (AZT/3TC) twice daily to people who can’t afford their own treatment. Everyone also receives education on general HIV knowledge, prevention, and adherence. The cohort began treatment with a median CD4 count of 119 cells/mm³ ($IQR$ 70 to 224 cells/mm³) and a median viral load of 5.5 logs (333,029 copies/mL, $IQR$ 5.0 to
5.8 logs). About one third had CDC class C disease.

The overall 24-week sub-400 response rate measured 53 percent, ranging from 56 to 76 percent at three sites (designated A, B, and C), but it reached a mere 14 percent at site D. Data from 22 people (44 percent) at that site did not get reported and thus was tagged as above 400 copies/mL. An analysis excluding unreported data found an overall success rate of 68 percent, including responses in 82, 62, and 86 percent at sites A, B, and C, and 25 percent at site D—so site D had problems besides missing data.

An adherence analysis involving 125 people yielded discouraging results, classifying one third as nonadherent. Nonadherence ranged from 19 to 51 percent. Median CD4 gains ranged from 63 cells/mm³ at site B to 129 cells/mm³ at site D, with an overall gain of 99 cells/mm³ (IQR 41 to 164 cells/mm³). People started therapy with nevirapine (NVP) plus AZT/3TC or stavudine (d4T)/3TC and had a CD4 count of 192 cells/mm³ and a viral load of 135,200 copies/mL (± 126,400 copies/mL SD). Mortality so far measures 7.2 percent among treated people and 11.9 percent among untreated people. Only a handful in each group—3.6 and 4.7 percent—have stopped coming back for checkups, a rate Leonardo Palombi and coworkers attribute to intensive counseling and peer support. Among 413 people treated for an average 113 days, 68 percent have a viral load below 50 copies/mL. The average CD4 count doubled. The DREAM team argued that baseline viral load “is crucial also in Africa.”

Dying

Perhaps the most revealing inquest into the effect of potent antiretrovirals came from Paula Munderi (Medical Research Council, Entebbe), who compared the antiretroviral-naive Entebbe cohort with Ugandans enrolled in the DART trial [abstract TuOrC1158]. Results showed that even people who start treatment with the lowest CD4 counts cheat death at a high rate, especially when compared with untreated individuals. And in DART they usually did so with a triple nucleoside/tide regimen, AZT, 3TC, and tenofovir disoproxil fumarate (TDF).

Munderi compared 456 people from the Entebbe cohort with 745 DART enrollees. Follow-up in the Entebbe group ran from May 1995 through January 1998 and in DART for one year after treatment began. Although no one in the Entebbe cohort got antiretrovirals, many benefited from cotrimoxazole for Pneumocystis pneumonia or isoniazid for tuberculosis (TB). In February 2003, DART started recruiting treatment-naive adults with a CD4 count under 200 cells/mm³ and followed them every four weeks to check adherence and treatment response.

Crude death rates measured 46 percent in the Entebbe group (211 of 456) and 3 percent (20 of 745) in DART (Table 5). The overall risk of death proved more than 10 times higher without antiretrovirals, even though some Entebbe cohort members got treated for pneumonia or TB and the analysis excluded cohort members with malignancies or severe acute disease.

Kids

A retrospective look at an antiretroviral rollout among 232 children in Botswana showed excellent responses and a trifling drug switch rate [abstract TuOrB1191]. But Haruna Jibril (Princess Marina Hospital, Gaborone) offered some evidence of rebounding viremia over 12 months of treatment.

### Table 4. CD4 gains through 18 months in MSF programs

<table>
<thead>
<tr>
<th>Months</th>
<th>Median CD4 gain (cells/mm³)</th>
<th>&gt;200 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>90 (IQR 50 to 131, n = 316)</td>
<td>31.6% (110 of 348)</td>
</tr>
<tr>
<td>12</td>
<td>162 (IQR 91 to 231, n = 260)</td>
<td>58.2% (171 of 294)</td>
</tr>
<tr>
<td>18</td>
<td>163 (IQR 115 to 273, n = 52)</td>
<td>57.4% (31 of 54)</td>
</tr>
</tbody>
</table>

Source: Médecins Sans Frontières, abstract ThPeB7179.
The Botswana-Baylor Children’s Clinical Center of Excellence began treating children with AZT/3TC or d4T/3TC plus NVP or efavirenz (EFV) in April 2002. Among 232 children treated for at least six months (and most for 12 months), 18 (7.8 percent) died. Nine of the 18 died within the first three months of therapy and another five between months three and six; many of them were probably desperately ill when therapy began. The 214 survivors also had advanced disease when Botswana started providing free drugs to all infected children under one year old; their CD4 percent averaged 15.2 percent and their viral load 404,845 copies/mL. The baseline CD4 numbers rose by an average 10.4 percent at month three, 13.9 percent at month six, and 16.2 percent at month 12.

The proportion of children with a viral load under 400 copies/mL stood at 84 percent by treatment month three, 85 percent at month six, and 82 percent at month 12. Average viral loads at those three points—7,331 copies/mL, 12,036 copies/mL, and 29,254 copies/mL—suggested a slow loss of virologic control. But so far clinicians have turned to a second-line regimen in only 29,254 copies/mL — suggested a slow loss of virologic control. But so far clinicians have turned to a second-line regimen in only 2.9 percent, and toxicity caused none of those switches. The usual second regimen is didanosine (ddI), d4T, and nelfinavir (NFV).

### Adhering
How well people in struggling countries will adhere with antiretroviral therapy fast became a flashpoint in debates over the speed of antiretroviral access. Until now, much of this debate has been rooted in the soggy ground of speculation. That will change as formal studies of adherence appear, as several did in Bangkok. Two take-away messages are that adherence at sites studied so far is no worse than in the West, and sometimes better, and that pill taking (as in rich countries) worsens with time. That news may come as no surprise, but some of the factors predicting adherence did raise eyebrows.

For starters, Cristina Hofer (HUCFF Universidade Federal do Rio de Janeiro) reached the counterintuitive conclusion that physician instruction on taking antiretrovirals imperils adherence, at least in two of Rio’s public primary care clinics [abstract WeOrB1319]. Hofer and colleagues approached 226 HIV-infected adults attending these clinics, and 220 agreed to answer adherence questions. One third of respondents were women, and 61 percent had formal education of eight years or fewer. Defining adherence as taking 95 percent or more of prescribed drugs in the preceding three days, Hofer rated 104 people adherent and 116 nonadherent. Self-reported adherence measured 81 percent, compared with clinician estimates of 75 percent for these people. Six factors favored poor adherence, while two promoted adherence in a multivariate analysis:

#### Favored poor adherence
- Feeling that antiretrovirals make you sick: odds ratio (OR) 3.16, \( P = 0.03 \)
- Family problems caused drug-taking difficulties: OR 3.0, \( P = 0.02 \)
- Doctor taught how to take antiretrovirals: OR 2.83, \( P = 0.01 \)

#### Did not favor poor adherence
- Financial problems: OR 1.84, \( P = 0.07 \)
- Number of times drugs taken daily: OR 1.6, \( P = 0.02 \)
- Years known to have HIV: OR 1.02 per year, \( P = 0.05 \)

Hofer proffered no hypotheses on why clinician counseling worsened adherence. Perhaps instructions from clinicians—rather than nurses or assistants—confused people. The results suggest that limited formal education does not hinder adherence; simply recognizing pictures of drugs made poor adherence significantly less likely.

In Senegal, as in wealthier whereabouts, adherence wanes as time flies, according to results presented by Alice Desclaux (French Cooperation/Multisectorial AIDS Control Program, Dakar) [abstract WeOrB1320]. But the estimated probability of high adherence (95 percent or better) in 159 people treated for four years in the Senegalese national program stood at a robust 78 percent (95 percent CI 0.74 to 0.81). Calculating adherence as the stated number of tablets taken times 100 divided by the number prescribed. Desclaux prospectively tracked the cohort from November 1999 through April 2004. They began treatment with a mean viral load of 5.44 logs and a mean CD4 count of 160 cells/mm³. Four in 10 people were unemployed, and 93 percent began treatment with no antiretroviral history. Twenty-two

### Table 5. Risk of death in antiretroviral-treated and untreated Ugandans

<table>
<thead>
<tr>
<th>Baseline CD4 cell/mm³</th>
<th>Entebbe cohort</th>
<th>DART trial</th>
<th>Relative risk</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 49</td>
<td>975.3 (796.8 to 1,193.8)</td>
<td>123 (71.3 to 211.7)</td>
<td>7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50 to 99</td>
<td>662.5 (509.8 to 860.9)</td>
<td>35.5 (11.4 to 110.0)</td>
<td>18.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>100 to 199</td>
<td>367.7 (286.1 to 472.6)</td>
<td>23.8 (8.9 to 63.4)</td>
<td>15.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>608.4 (531.6 to 696.3)</td>
<td>55.8 (36.0 to 86.5)</td>
<td>10.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

95% CI = 95 percent confidence interval; p-y = person-years.

Source: Paula Munderi, abstract TuOrC1158.
people (14 percent) died during follow-up, and seven (4 percent) stopped their HIV meds.

Adherence averaged a sturdy 90.2 percent over the four-year study. Eighty participants (50 percent) got an adherence head-start because they began therapy in clinical trials, though the trial period accounted for only 18 of 54 observed months. Adherence did slip inexorably with time. In a multivariate analysis with the first 12 months as a baseline, the risk of poor adherence rose by 46 percent during months 13 through 24, by 57 percent during months 25 through 36, and by 66 percent after month 36. Three other variables predicted wobbly adherence in this analysis:

• Symptomatic disease (CDC stages B or C) when treatment began: odds ratio (OR) 0.30, $P = 0.003$

• Monthly antiretroviral cost more than $18: OR 0.61, $P = 0.001$

• PI-containing therapy: OR 0.70, $P = 0.08$

The first of those findings runs counter to some Western studies, in which symptomatic disease inspires better adherence. Disease progression may have reached a more acute stage before treatment in the Senegalese cohort, or perhaps clinicians lacked the means to treat those complications.

Probably the most thorough resistance analysis came from Jessica Oyugi (University of California, San Francisco), who juggled four adherence yardsticks in 97 people starting their first antiretrovirals [abstract WeOrB1323]. Everyone took a fixed-dose combination of d4T, 3TC, and NVP (Triomune or Maxivir) for which the median viral load of 5.47 logs.

Through 24 months of follow-up, 10 percent stopped treatment (usually when starting TB therapy), and 10 percent died. Among the others, 58 percent had a viral load below 400 copies/mL. The four adherence scales proved remarkably consistent and suggested only slight slippage from week 12 to week 24 (Table 6).

Can clinicians get children to take antiretrovirals on time? Yes, reported Rawiwan Hansudewechakul (ChiangRai Regional Hospital, Thailand), with careful planning and plenty of backup [abstract WeOrB1324]. Before even starting treatment for 60 children, Rawiwan and coworkers scheduled two clinic visits and one in the home, while assigning two “caretakers” to oversee directly observed therapy for each child. Children also wear alarm watches and use seven-day pill boxes to stay on schedule.

Gauging adherence by pill count and several self-report techniques, Rawiwan rated 90 percent of children 95 percent adherent through several months of follow-up. The results are especially encouraging because most children take a fixed-dose adult combination of d4T, 3TC, and NVP that has to be pared into pediatric-dose portions. The Thai Government Pharmaceutical Organization (GPO) will start making pediatric fixed-dose combos next year.

### Table 6. Adherence by four methods in 97 self-paying Senegalese

<table>
<thead>
<tr>
<th>Percent adherence</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three-day self-report</td>
<td>92.7</td>
<td>90.3</td>
</tr>
<tr>
<td>Visual analog scale</td>
<td>91.0</td>
<td>89.4</td>
</tr>
<tr>
<td>Unannounced home pill count</td>
<td>90.8</td>
<td>84.4</td>
</tr>
<tr>
<td>Electronic medication event monitoring</td>
<td>91.1</td>
<td>88.4</td>
</tr>
</tbody>
</table>

Source: Jessica Oyugi, abstract WeOrB1323.

### INTERMEZZO

(Side Effects)

The elephant charged with murder after parading through the conference’s opening pageant (see “Elephants” above) may have gotten a bad rap, according to investigative reporters for The Nation. Allegations that the beast hoisted a helpless construction worker with its trunk, then slammed him into the ground, killing him, lost credibility as the police inquest continued. Fresh evidence suggested that the construction worker, emboldened by alcohol after a day’s labor, willfully harassed the hard-working pachyderm by trying to cut hairs from its tail for a talisman. This ticklish operation, perhaps best left to the stone-cold sober, apparently inspired the leviathan’s ire and provoked the fatal attack.

The XV International AIDS Conference did not explore the talismanic merits of tail hair. But it did pursue the nonstop search for philters that may forestall antiretroviral side effects, and it offered new insights on still-tenebrous links between HIV, its treatments, and toxicity. In this arena the epidemics of West and East remain a hemisphere apart. Although early antiretroviral research in lands of limited access dutifully record treatment’s depredations and resulting dropouts, the experience from site to site—with the possible exception of Bangkok itself—remains too brief to pin down long-term upshots.

Nothing could be less true in developed countries, where nearly a full decade has elapsed since the dawn of potent potpourris. And the Bangkok conclave offered several long-term over-the-shoulder audits.

#### Swiss risk

An illuminating analysis from the Swiss HIV Cohort Study found an overall drop in treatment-related side effects when comparing 340 people eyed once in 1999 and once in 2003 [abstract WePeB5949]. Olivia Keiser (Swiss HIV Cohort Study Data Center, Lausanne) traced the lower toxicity risk to evolving prescribing patterns and perhaps side effect remedies such as antilipid balms.

Although median treatment length jumped from 21 months in 1999 to 45 months in 2003, prevalence of antiretroviral-related clinical toxicities dropped from 67 percent to 53 percent over that span ($P < 0.001$). The rate of drug-related lab abnormalities crept from 42 percent in 1999 to 44 percent in 2003, a nonsignificant change.

Part of the clinical improvement may reflect toxicity-induced treatment breaks taken during these four years by 38 percent of people studied. In all, 69 percent of the cohort suspended therapy for some reason during that period. But the easing toxic burden also tracks with a decided shift in regimen planning, marked by the dumping of d4T and PIs (Table 7).

The percentage of people with high lipids dropped, perhaps because of the shift from PIs to NNRTIs and use of lipid-lowering drugs. And fewer people had nausea or diarrhea in 2003 than in 1999. But rates of fat abnormalities—probably reflecting accruing treatment experience—rose.
Table 7. Changing Swiss prescribing patterns: 1999 to 2003

<table>
<thead>
<tr>
<th>Percent taking</th>
<th>1999</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI-based regimen</td>
<td>76</td>
<td>42</td>
</tr>
<tr>
<td>NNRTI-based regimen</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>NRTI-only regimen</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>Stavudine</td>
<td>50</td>
<td>22</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>48</td>
<td>65</td>
</tr>
<tr>
<td>Abacavir</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>Indinavir</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

Source: Olivia Kesar, abstract WePe5949.

Bone death

Research has not nailed down the cause of osteonecrosis in people with HIV. Most work finds no link between bone death and antiretrovirals,15-18 but one cohort study did.19 The biggest study so far, from the French Hospital Database on HIV, sided with the minority report in blaming treatment for eroding bone cells [abstract ThOrB1358]. Among 56,259 people embraced by the database from 1996 through 2002, Murielle Mary-Krause and colleagues turned up 122 cases of osteonecrosis. Dividing risk factors into two groups (see note 20), they found that 87 percent had at least one group-one risk, 58 percent had at least one group-two risk, and 54 percent had risk factors from both groups. Nadir CD4 count proved substantially lower in people with (78 cells/mm³, IQR 18 to 168 cells/mm³) versus those without osteonecrosis (180 cells/mm³, IQR 60 to 316 cells/mm³). In a multivariate analysis that adjusted for nadir count, age, gender, HIV transmission risk group, and AIDS-defining diagnoses, the French team charted a relentlessly rising risk of osteonecrosis with longer therapy:

- Not exposed to HAART (reference group): 1.0
- Fewer than 12 months: relative rate (RR) 2.5, 95 percent CI 1.1 to 5.7
- 12 to 24 months: RR 4.7, 95 percent CI 2.2 to 10.1
- 24 to 36 months: RR 4.6, 95 percent CI 2.1 to 10.2
- 36 to 48 months: RR 5.6, 95 percent CI 2.5 to 12.4
- 48 to 60 months: RR 6.5, 95 percent CI 2.8 to 14.9
- 60 months or more: RR 6.3, 95 percent CI 2.6 to 15.3

The incidence of osteonecrosis remained low, even in people treated for five years or more, but it rose inexorably as the treatment clock ticked, from 1.2 cases per 10,000 person-years for treatment-naive people, to 3.4 cases for those treated less than one year, to 8.0 cases for those treated for 36 to 48 months, and to 10.8 cases for those treated for 60 months or more.

Mary-Krause argued that notification bias did not account for the rising incidence in recent years because diagnoses did not burgeon after clinicians perceived necrosis as a threat. And she maintained that duration of treatment did not simply reflect duration of HIV disease because of the statistical adjustment for nadir CD4 count.

An Argentine case-control study, on the other hand, chalked up a significantly briefer treatment in people with osteonecrosis compared to those without [abstract MoPeB3271]. As these researchers observe, though, that finding could reflect a selection bias inherent in single-site studies like this one.

Edgardo Bottaro (Hospital General de Agudos Donacion F. Santojanni, Buenos Aires) tallied 12 new cases of osteonecrosis among 2,300 people with HIV infection seen between November 1998 and March 2003 for an incidence of 0.52 percent. As in the French study, CD4 nadir proved lower in the people with osteonecrosis (60.8 versus 144.2 cells/mm³, P = 0.06). Significantly more of those with osteonecrosis used corticosteroids (75 percent versus 25 percent, P = 0.006), and significantly more had AIDS (100 percent versus 42 percent, P < 0.001). But the osteonecrosis group logged a shorter average time taking a potent regimen (35.6 versus 55.1 months, P = 0.006) and—most surprising—a shorter average time since HIV diagnosis (38 versus 76.5 months, P = 0.028).

D and kids’ bones

A study of 20 girls and 20 boys in New York City rated nine (23 percent) insufficient in vitamin D (between 12 and 20 ng/mL 25-hydroxyvitamin D) and three (7 percent) deficient (less than 12 ng/mL 25-hydroxyvitamin D) [abstract TuPeB4467]. Stephen Arpadi (St. Luke’s-Roosevelt Hospital Center) found a significant correlation between 25-hydroxyvitamin D and spine bone mineral density z-score (P < 0.05) in a multiple regression model controlling for age, race or ethnicity, gender, height, weight, viral load, CD4 percent, and sexual maturation.

The study included 23 black and 17 Hispanic children with a mean age of 11 years, a mean body mass index of 19.4 kg/m², and a mean height of 150 cm. Nineteen (48 percent) had taken one or more PI, and 17 (47 percent) had taken one or more NNRTI. Their viral load averaged 22,540 copies/mL and their CD4 tally 30 percent. Mean 25-hydroxyvitamin D stood at 27.2 ng/mL (±12.2 ng/mL), within the normal range of 20 to 65 ng/mL, but 21 children (52.5 percent) were below the normal range.

Arpadi stressed that “vitamin D status is a significant predictor of measures of bone mineral density” in children with HIV.

Heart stoppers

Three insightful studies weighed cardiovascular risks and markers in representative cohorts, including the Women’s Interagency HIV Study (WHIS), which failed to tie PI therapy to heart disease in a relatively young, mostly nonwhite group [abstract MoPeC3592]. The cohort included 862 women taking a PI for at least six months, 362 women not taking a PI, and 340 women without HIV infection. The median age was 42 years, 56 percent were black, 25 percent Hispanic, and 16 percent white. Researchers excluded women with a history of cardiovascular disease and relied on self-reports of myocardial infarction (MI), congestive heart failure (CHF), cardiovascular accident, or angina.

From October 2000 through October 2002, the risk of the four heart disease endpoints did not differ between the PI group and the non-PI group. Arjun Dutta (Howard University, Washington, DC) reported that this null result persisted in a multivariate analysis factoring in age, gender, and smoking status. Nor did the incidence
of cardiovascular disease differ between women with HIV and those without HIV.

A three-year analysis of 5,907 members of the Swiss HIV Cohort Study found that 19 percent had a moderate (15.5 percent) or high (3.3 percent) 10-year risk of coronary heart disease (CHD) figured by the Framingham algorithm (Table 8) [abstract WePeB5878]. The risk proved even steeper among men 40 years old or older, with 34.2 percent at moderate risk and 7.4 percent at high risk. In comparison, 4.7 percent of women over 39 had a moderate risk and 0.4 percent had a high risk.

Tracy Glass (University Hospital Basel) tallied heart trends in 4,079 men and 1,828 women who filled in cardiovascular questionnaires and had related lab tests around the same time. Smoking ranked as the most prevalent risk factor, in 59 percent overall and varying little with age or gender (Table 8). Men over 40 had the highest prevalence of diabetes (4.7 percent), high blood pressure (32.1 percent), total cholesterol above 6.2 mmol/L (26.1 percent), and metabolic syndrome (19.2 percent). Women over 39 also had ample rates of metabolic syndrome (15.8 percent) and total cholesterol above 6.2 mmol/L (25.1 percent).

A comparison of 40 people taking a PI and 80 taking an NNRTI in the United States found significantly higher coronary artery calcium scores—a signal of subclinical atherosclerosis—in the PI group [abstract ThOrB1355]. This single-center study also logged a rapid rise in another marker, carotid intima media thickness, in both groups.

Gerald Pierone (AIDS Research and Treatment Center, Fort Pierce, Florida) tested 40 people who took a PI, 40 who took NVP, and 40 who took EFV for at least three years. People in the NNRTI group could have taken a PI earlier, but not for three years. The PI group included significantly more men (90 percent, P = 0.03) than the groups taking NVP (73 percent) or EFV (66 percent), while baseline total cholesterol and low-density lipoprotein (LDL) cholesterol were significantly higher with NVP than a PI (P = 0.038 and 0.012). Other cardiovascular risk factors didn’t differ from group to group. Because Pierone saw no marked differences between people taking NVP versus EFV, he combined those groups to compare them with PI takers.

Twenty-one of 40 people on PIs (52 percent) had a coronary artery calcium score above 0, compared with 21 of 80 (26 percent) taking a nonnucleoside. In a multivariate analysis PI therapy raised the risk of a positive score 2.32 times. Nine of 40 PI-treated people (22 percent) had a calcium score above 100, compared with six of 80 taking NVP or EFV (7 percent) to yield a 9.56 times higher risk with PI therapy. Three other variables boosted the risk of a calcium score above 100: older age, more years living with HIV, and hypertension.

Pierone saw no significant difference in carotid artery intima media thickness when comparing the PI and NNRTI groups. But a longitudinal analysis showed that intima media thickness bolted from 1.04 to 1.14 cm in one year among people taking NVP, and from 0.97 to 1.15 cm among people taking a PI. The apparently faster thickening with PI therapy did not reach statistical significance.

**Pre-eclampsia**

A few years ago Oriol Coll and coworkers at the University of Barcelona Hospital Clinic started noticing a growing rate of pre-eclampsia (defined as blood pressure at or above 140/90 mm Hg and proteinuria at or above 300 mg/24 hours) and fetal death among pregnant women with HIV infection [abstract ThOrB1359]. To probe for risk factors, he compared rates of pre-eclampsia and infant death in 472 HIV-infected women who gave birth from November 1985 through July 2003, 122 of whom had an unadjusted analysis (P < 0.001), while active injecting drug use made fetal death 8.6 times more likely (P < 0.001).

Looking only at 472 women with HIV, Coll calculated a lower risk of pre-eclampsia with smoking (AOR 0.05, P = 0.005) and a higher risk with a longer time since HIV diagnosis (AOR 1.02 per month, P = 0.005). Older age hiked the risk of fetal death 1.18 times per year (P = 0.017) in an unadjusted analysis, as did time since HIV diagnosis (OR 1.02, P = 0.001) and HAART before pregnancy (OR 7.9, P = 0.005).

Rating risk factors only among 122 women who took a potent antiretroviral regimen before pregnancy, Coll found again that smoking trimmed the odds of pre-eclampsia or fetal death (OR 0.285, "HAART group" women who gave birth since 1998, and a global population of 8,768 women who gave birth since January 2001. All women studied had normal blood pressure before pregnancy.

Rates of pre-eclampsia and fetal death measured 2.9 and 0.5 percent in the global population, 1.9 and 1.7 percent in the 1985-2003 HIV group, and 6.6 and 4.1 percent in the 1998-2003 HIV group. In the combined global and HIV groups, the risk of pre-eclampsia proved lower among women who smoked (adjusted odds ratio [AOR] 0.65, P = 0.01) and in multipartous women (AOR 0.76, P = 0.04). HIV infection inflated the risk of pre-eclampsia 4.9 times (P < 0.001). HIV boosted the risk of

### Table 8. Smoking and CHD risk in the Swiss HIV Cohort Study

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Men &lt;40</th>
<th>Men ≥40</th>
<th>Women &lt;40</th>
<th>Women ≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>5,907</td>
<td>2,050</td>
<td>2,029</td>
<td>1,321</td>
<td>507</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>59.0</td>
<td>66.3</td>
<td>53.7</td>
<td>58.0</td>
<td>52.9</td>
</tr>
<tr>
<td>Moderate risk * (%)</td>
<td>15.5</td>
<td>9.2</td>
<td>34.2</td>
<td>0.8</td>
<td>4.7</td>
</tr>
<tr>
<td>High risk * (%)</td>
<td>3.3</td>
<td>1.9</td>
<td>7.4</td>
<td>0.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**CHD = coronary heart disease.**

*Calculated by the Framingham algorithm; moderate 10 to 20 percent, high greater than 20 percent. Source: Tracy Glass, abstract WePeB5878.
IAPAC Monthly September 2004

...has not been a single case of mother-to-child HIV transmission since it started treating pregnant women with potent therapies, and he doesn’t think the risk of pre-eclampsia outweighs the benefit of antiretroviral therapy. But it merits further study at other sites.

Genes, CD4, NVP

Recent research established the risk of early immune-mediated reactions to NVP in people—especially women—starting therapy with a CD4 count above 200 cells/mm³. Now enterprising pharmacogenetic work from Simon Mallal’s lab at the Royal Perth Hospital suggests markers that may predict a heightened risk of such reactions, at least among Caucasians [abstract LbOr13].

Mallal rated HLA markers in 241 people taking NVP, 85 percent of them white and only 11 percent women—not enough to discern gender-based differences. A clinician who did not know the HLA typing results identified 26 cases of early allergic reactions to NVP in the first 12 weeks of treatment, including separate or combined cases of rash in 21, fever in 11, and hepatitis in nine. Weighing the risk of all these reactions, Mallal found a three times higher risk with the HLA-DRB1*0101 haplotype (P = 0.035). Excluding cases of isolated rash, he figured a 4.9 times higher with that haplotype (P = 0.009). Excluding isolated rash in people with a CD4 percent topping 25, he found an 18.2 times higher risk with the same haplotype (P = 0.00004).

Those findings suggest a bond between better immune function and genetic factors in predisposing white people to NVP hypersensitivity reactions. Mallal reckoned that screening Caucasians for HLA markers may avert one of 14 potentially fatal hypersensitivity reactions in people with a CD4 percent topping 25.

Rosier results

A 48-week Australian placebo-controlled trial of rosiglitazone in people with lipodystrophy appeared to nullify any notion that this insulin sensitizer can fix fat abnormalities in HIV-infected people with lipodystrophy. But the Bangkok conference yielded yet another small study that did record subcutaneous fat gains—after 24 weeks and with 4 mg daily instead of the 8 mg the Australians used [abstract WePeSB9542]. As in earlier HIV-related studies of this agent, however, triglycerides and cholesterol climbed.

T. Feldt (Heinrich Heine University, Düsseldorf) gave rosiglitazone to 20 people with severe lipodystrophy while taking stable antiretroviral regimens. Twenty-four weeks later the group enjoyed significant improvements in percent leg fat (12.93 to 15.03 percent, P < 0.001), subcutaneous adipose tissue (113.7 cm² to 125.3 cm², P = 0.04), and abdominal circumference (94.7 cm to 91.68 cm, P = 0.04). Feldt also saw modest improvements in percent trunk fat (21.67 to 22.84 percent, P = 0.1) and percent total fat (17.79 to 18.52 percent, P = 0.08).

Total cholesterol rose from 248 to 281 mg/dL (P = 0.006) over 24 weeks, while triglycerides nosed up nonsignificantly from 301 to 351 mg/dL (P = 0.1). Insulin sensitivity improved, but not significantly. Notably, 12 of 20 study participants (60 percent) claimed to see comelier body contours, whereas “HIV experts” saw no apparent changes on before-and-after photos. Feldt did not report the number of women studied; the Australian trial included only a few women.

Rituximab and CDE for lymphoma

The anti-CD20 monoclonal antibody rituximab plus chemotherapy counters high-grade lymphoma better than chemotherapy alone in the general population. The same proved true for antiretroviral-treated people with HIV-related non-Hodgkin lymphoma (NHL), reported Cecilia Simonelli (National Cancer Center, Aviano, Italy), although the risk of bacterial infection was high [abstract ThOrB1404]. Simonelli and colleagues treated 60 men and 14 women with 375 mg/m² of intravenous rituximab, followed by four days of continuously infused CDE: cyclophosphamide (187.5 mg/m²/day), doxorubicin (12.5 mg/m²/day), and etoposide (60 mg/m²/day). She repeated the four-day infusions every four weeks for up to six cycles. The study group began treatment at a median age of 38 years and a median CD4 count of 161 cells/mm³. Fifty-six (84 percent) had a detectable viral load. All took antiretrovirals throughout NHL therapy.

Six people (8 percent) had to stop chemotherapy and 31 (42 percent) needed a lower dose. After a median follow-up of 16 months, 52 (70 percent) had a complete response, four (5 percent) had a partial response, and 18 had progressive disease. Seven people with a complete response suffered a relapse, and seven contracted bacterial pneumonia because of treatment-induced neutropenia.

Simonelli recorded 10 new AIDS diagnoses (13.5 percent), and 26 people (35 percent) died, primarily because of NHL progression. A multivariate analysis tied three factors to a worse response: Burkitt’s lymphoma (versus diffuse large-cell lymphoma), infection through gay sex, and a detectable viral load. Simonelli suggested that people with Burkitt’s lymphoma need more aggressive NHL therapy.

Long-lasting liposuction

Liposuction and other maneuvers to banish buffalo hump have met with limited success because of a high recurrence rate. But Cristina Gervasoni (University of Milan) reported only one relapse among four women and 14 men who had liposuction or classic surgical removal of dorsal neck fat [abstract WePeBS9538]. Sixteen of the 18 people taking a PI regimen when the buffalo hump appeared...
Anal PAP for lesions in gay men

Anal PAP smears had a 95 percent sensitivity for spotting anal dysplasia in men who have sex with men screened at San Francisco General Hospital since June 2001, reported Anthony Lee [abstract THO81407], but specificity measured only 30 percent. A highly sensitive test can rule out disease, Lee explained, but low specificity renders the test unreliable at ruling in disease, so a positive PAP calls for further testing.

Lee and colleagues screened 417 gay men with anal PAPs between June 2001 and December 2003. The PAPs proved normal in 189 (46 percent) but showed atypical squamous cells of uncertain significance (ASCUS) in 121 (29 percent), low-grade dysplasia in 85 (20 percent), high-grade dysplasia in 18 (4 percent), and carcinoma in four (0.9 percent).

Of the men with abnormal PAP smears, 163 had paired biopsies collected during high-resolution anoscopy. Biopsies proved normal in 31 (19 percent) while detecting ASCUS in three (2 percent), low-grade dysplasia in 79 (48 percent), moderate dysplasia in 28 (17 percent), high-grade dysplasia in three (2 percent), severe dysplasia in 13 (8 percent), and carcinoma in six (4 percent).

Lee noted that gay men have about a 37 times higher risk of anal cancer than the general population. He called follow-up of abnormal PAP results with high-resolution anoscopy and biopsy “crucial.”

saw no improvement 10 to 24 months after switching to a nonnucleoside. At the time of surgery their age ranged from 35 to 68 years (median 43 years), their CD4 counts from 101 to 926 cells/mm³ (median 573 cells/mm³), and their viral loads from undetectable (in 14) to 200,000 copies/mL. Fifteen people had liposuction preceded by local infiltration of saline solution, cold adrenaline (4º C), and lidocaine. Three had classic surgical fat removal.

After 18 to 40 months of follow-up (median 24 months), buffalo hump recurred in only one person (5.5 percent) three months after liposuction. This person underwent a second procedure, with good results so far.

ANTIRETROVIRAL STRATEGIES

(North/West)

The questions that vex antiretroviral planners in rich versus poor countries differ starkly. Starting from a small patch of common ground—what regimens will rein in the retrovirus with the fewest toxic pocks and shocks?—research races down divergent paths depending on geography. In countries where antiretrovirals have done their best, and worst, for more than 15 years, the top question has become: How can I get this done with less? That question confronted Bangkok conference attendees in many guises:

• Can I prescribe just a boosted PI?
• Which once-daily regimens work best?
• Can I start strong, then cut back?
• What’s the safest way to suspend therapy?

In other countries, despite stuttering steps to wider access, the key question remains: How can I get these drugs in the first place? But if the drugs are in hand, the most exigent question becomes: Is first-line NNRTI therapy really the best choice—especially if I’ve already given this woman or child NVP to prevent transmission of HIV?

The rest of this article explores some suggested answers.

Only Kaletra OK?

Since the debut of structured treatment interruptions (STIs), no treatment notion has garnered more regard than boosted PI “monotherapy.” So far that means high-dose SQV/RTV24 or RTV-boosted lopinavir (LPV), IDV, or SQV. Four conference reports brought news of stand-alone LPV/RTV (Kaletra)—one as a day-one option, and three as maintenance therapy after a traditional triple. Another study (reviewed in the next “South/East” section) looked at solo SQV/RTV (600/100 mg twice daily) as an induction regimen.

In the pace-setting SQV/RTV trial, only 28 of 141 people (20 percent) had to add NRTIs through 48 weeks,24 but the doses tried in that study (400/400 mg, 400/600mg, or 600/600 mg twice daily, or 400/400 mg three times daily) would not be used today because of RTV toxicity. In an IDV/RTV maintenance tryout published this year, Swiss clinicians saw no virologic failures—but a few blips above 25 copies/mL—in 12 people who tried dose-adjusted IDV/RTV maintenance for 48 weeks after tight control with IDV/RTV plus nucleosides.25

Joseph Gathe (Therapeutic Concepts, Houston) offered a 48-week analysis of solo LPV/RTV as first-line therapy for 28 men and two women with fairly advanced disease signaled by a mean CD4 sum of 169.5 cells/mm³ and a mean viral load of 262,020 copies/mL [MoOrB1057]. Twenty-one (70 percent) had a CD4 count under 200 cells/mm³. Gathe based the dose on weight:

• 400/100 mg twice daily if less than 70 kg
• 533/133 mg twice daily if more than 70 kg

After 48 weeks, 18 people (60 percent) had a viral load below 50 copies/mL in a noncompletor-equals-failure analysis. Ten people dropped out of the study because of virologic failure (two), gastrointestinal side effects (two), nonadherence (two), missed visits (two), deportation (one), or hepatitis B virus (HBV) infection (one). Two other people needed extra antiretrovirals to slow HIV. Among the four people in whom LPV/RTV alone failed to push the viral load below 50 copies/mL, Gathe reported that three suspended treatment or dropped to one dose daily because their insurance coverage ran out. In the single apparent case of full-treatment virologic failure, only the L63P polymorphism emerged in viral protease. Among people who stayed in the study, the average CD4 count climbed 317 cells/mm³.

José Arribas (Hospital La Paz, Madrid) and colleagues from three other hospitals tried LPV/RTV (400/100 mg twice daily) as maintenance therapy for 21 people who logged a viral load below 50 copies/mL with LPV/RTV plus two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) [abstract TuPeB4486]. Another 21 with sub-50 loads on LPV/RTV triple therapy continued the three-drug regimen in this randomized trial. Everyone entered the study with a viral load below 50 copies/mL for at least six months; no one had endured a virologic failure while taking a PI; and everyone had taken LPV/RTV triple therapy for more than one month.

The Only-Kaletra (OK) arm had a pre-HAART load of 5.11 logs, compared with 4.93 logs in the continued-triple arm. Median months with a viral load below 50 copies/mL favored the OK arm (28.6 versus 15.7 months), as did nadir CD4 count (139 versus 90 cells/mm³). Fifteen people in the OK arm and 18 in the triple arm had taken an earlier PI.

Defining maintenance failure as back-to-back RNAs above 500 copies/mL or a therapy change, Arribas found that only Kaletra was not okay for three people (14 percent) with protocol-defined failure by
week 24, and another person in the OK arm stopped keeping appointments. No primary PI mutations popped up during these maintenance failures. All 21 people in the control arm remained failure free.

Arribas tracked down only one trait that distinguished failure from continued suppression in the OK arm—fewer days with a viral load under 50 copies/mL before maintenance (median 218, range 208 to 229 days, for failures, versus median 1,095, range 277 to 2,613 days, $P = 0.002$). All three people with a maintenance failure beat HIV back below the 50-copy cutoff by adding the same NRTIs they had stopped. Three OK candidates and no control arm members had blips above 50 copies/mL.

Why did maintenance LPV/RTV fizzle for three people despite the apparent lack of resistance? Arribas suggested several possibilities:

- Undetected low-level replication at baseline (a reasonable hypothesis given the greater blip and failure frequency in the OK group)
- Minority populations of resistant virus (ultrasensitive techniques in many studies implicate minority mutants in failures of various regimens)
- Host factors (such as LPV/RTV failure to breach certain sanctuaries or overexpression of drug efflux pumps)

A fourth possibility proffered at this year’s XIII International HIV Drug Resistance Workshop is emergence of PI resistance mutations in viral gag.$^{26}$

Another study of LPV/RTV maintenance, this one nonrandomized, involved 18 people naive to PIs who had kept their viral load under 75 copies/mL while taking NVP or EFV plus two NRTIs [abstract TuPeB4595]. They swapped the NNRTI for LPV/RTV while continuing the NRTIs for two weeks, then dropped the NRTIs.

After 24 weeks of follow-up Gerald Pierone (AIDS Research and Treatment Center, Fort Pierce, Florida) counted three dropouts due to diarrhea and one to viral rebound. A primary protease mutation, M36I, appeared in the rebounder, who regained sub-75 control with a triple regimen including NVP. Another person met the study definition of virologic failure with two consecutive loads topping 400 copies/mL. Two other people had blips. Pierone blamed faulty adherence for the failures and blips. The four dropouts and one failure add up to a 72 percent intent-to-treat success rate at the 75-copy mark.

A third LPV/RTV maintenance study involved 19 people with an undetectable load for more than nine months, a nadir CD4 count above 150 cells/mm$^3$, no PI resistance, and no more than one viral load above 400 copies/mL while taking potent antiretrovirals [abstract TuBeB4577]. Peter Ruane (Tower Infectious Diseases, Los Angeles) recruited volunteers from people taking LPV/RTV and reaching a trough above 3.0 µg/mL—two standard deviations above median troughs in LPV/RTV pharmacokinetic studies. LPV troughs in his 19 patients ranged from 3.26 to 11.93 µg/mL.

In short, Ruane picked people with a fine chance of keeping HIV under wraps with LPV/RTV monotherapy, but four people had a viral load above 75 copies/mL within six months. Two of these readings were blips blamed on bad adherence, and two were full-fledged rebounds—one because of nonadherence and one for cryptic reasons not tied to resistance. Four people pulled out of the study, one because of gut pain, one with second thoughts about the tactic, and two because they stopped coming for follow-up. Adding up these virologic ups and downs (and counting the blippers as responders), one gets a noncompleter-equals-failure response rate of 68 percent. Counting the blippers as failures yields a response rate of 53 percent. In the 15 people who didn’t drop out, triglycerides soared 90 percent in 24 weeks.

What can be made of this stratagem so far? To begin, RTV-boosted monotherapy should not become a try-at-home tactic. Even though clinicians launched all four studies mentioned here, their findings should persuade all prudent practitioners to await results of larger ongoing studies. Because uncounted people with HIV will read this and other reports of these studies, clinicians should also warn everyone prescribed a boosted PI not to try monotherapy on their own. Why?

First, these studies are all small, and the only randomized effort, by Arribas, showed that classic triple therapy works better.

Second, although primary protease mutations usually did not emerge during protocol-defined failures, some shortcoming of PI monotherapy must explain these failures. That’s why researchers report intent-to-treat analyses.

Third, a primary protease mutation did arise in Pierone’s maintenance arm, and that person had to switch back to NVP-based triple therapy. This individual would probably respond to a boosted-PI regimen, but it’s better to have no PI mutations at all. The International AIDS Society-USA lists the M36I mutation as a favored escape route from IDV, RTV, and NFV.$^{27}$

Fourth, one rationale cited to support PI/RTV monotherapy is improved adherence, but adherence is not a categorical consequence of such regimens. They all depend on twice-daily dosing, which could make them less preferable than numerous once-a-day anodymes. Gathe, Ruane, and Pierone all impeach poor adherence for virologic vicissitudes in their studies.

Fifth, another motive for PI monotherapy—fewer side effects—didn’t pass muster with one person in Ruane’s study, two in Gathe’s, and three in Pierone’s who quit LPV/RTV because of gastrointestinal gyrations. Others who “withdrew consent” or were “lost to follow-up” may have bailed out because of intolerance. Also, despite its durable potency, LPV/RTV cranks up lipids relentlessly and gums up glucose metabolism.

Neither Gathe nor Arribas reported metabolic meanderings in their studies, an omission that should be rectified. Pierone did track lipids and glucose, and his findings hold no surprise. Two people who started LPV/RTV maintenance with hyperglycemia had diabetes by week 24. Although both remained in the study and responded to diet and antidiabetics, neither of those remedies adds much to quality of life. Three people had to start lipid-lowering drugs during the study, and two already taking lipid limiters upped their doses. Among nine people who didn’t start statins or fibrates, mean triglycerides jumped from 109 to 159 mg/dL in 24 weeks. Triglycerides also skittered upwards in Ruane’s group.

Finally, the higher blip rate recorded by Arribas and Pierone with solo LPV/RTV may be a whisper of weaker suppression.

In sum, a dispassionate critic may conclude that LPV/RTV has fallen short so far. Still, a cross-study comparison—noxious to all but the curious—shows that Gathe’s 60 percent 48-week intent-to-treat success comes close to the 67 percent rate chalked up in 653-person randomized comparison of LPV/RTV and NFV, both
with d4T/3TC, in treatment-naïve people. Those itching to play LPV/RTV solitaire before seeing Abbott Laboratories’ results should ask themselves whether adding once-a-day TDF/emtricitabine (FTC) or 3TC/abacavir (ABC) is so onerous, or whether it may be easier for people to take.

**EFV qd**

*Quaque die* (qd), or once-daily, EFV has proved a smooth third wheel to many a qd binucleocycle. (An exception may be once-a-day ddI/TDF with EFV, results of a small randomized trial suggest.) Two studies reported in Bangkok—both supported by Bristol-Myers Squibb—rang up good 48-week results with EFV and extended-release d4T (d4T-XR)/3TC or ddI/3TC.

Compared with the 60 percent noncompleter-equals-failure rate in Gathe’s LPV/RTV pilot (see preceding section), a multicenter group posted a 71 percent success rate by the same measure in a study of once-daily d4T-XR, 3TC, and EFV [abstract TuPeB4510]. And this study was larger, with 70 participants starting their first antiretrovirals. Dushyantha Jayaweera (University of Miami) and colleagues from five other clinics counted 50 people with viral loads under 50 copies/mL in the 48-week noncompleter analysis and 50 of 53 (94 percent) under 50 copies in an as-treated analysis.

These volunteers began treatment with a higher mean CD4 count than those in the LPV/RTV study (351 cells/mm3) and with a lower viral load (4.54 logs). The protocol barred anyone with hepatitis, a history of pancreatitis or bilateral peripheral neuropathy, and “certain other” unnamed clinical or lab abnormalities.

Sixteen people (23 percent) never made it to week 48. Five dropped out with side effects, five withdrew consent, three stopped keeping appointments, and three left for other reasons. Three people (4 percent) suffered neuropathy, and signs of lipodystrophy appeared in one. No one suffered symptomatic high lactates, lactic acidosis, or pancreatitis. The total-to-high-density lipoprotein (HDL) cholesterol ratio dropped 33 percent (P < 0.01), though triglycerides climbed from 117 to 144 mg/dL (P < 0.01).

A similar study of once-a-day ddI, 3TC, and EFV met with similar success [abstract WePeB4594]. Douglas Ward (Dupont Circle Physicians Group, Washington, DC) and confreres from three other centers found that 52 of 65 people (80 percent) had a 48-week sub-50 load in a noncompleter analysis, while 52 of 53 (98 percent) hit that RNA mark in an as-treated analysis. In a noncompleter analysis of 28 people starting treatment with more than 100,000 copies/mL, the 50-copy response rate at 48 weeks measured 89 percent.

The 65 enrollees started swallowing once-daily drugs with a mean viral load of 4.8 logs and a mean CD4 total of 311 cells/mm3. So, again, this group began treatment in better shape than Gathe’s LPV/RTV cohort. Ward and colleagues excluded people with hepatitis, pancreatitis, or “failure to fall within acceptable laboratory or clinical parameters.”

A dozen people (18 percent) left the study before 48 weeks, three because of side effects, three with withdrawn consent, and six for other reasons. Many of the grade 2 to 4 side effects—dizziness, spooky dreams, insomnia—can probably be traced to EFV. Two people had grade 1 peripheral neuropathy, and three endured grade 3 to 4 lipase lifts, but none wound up with clinical pancreatitis. The total-to-HDL cholesterol ratio slipped from 4.17 to 3.75, a nonsignificant shift, while median baseline triglycerides shimmied from 107 to 129.5 mg/dL.

**Three or four nukes?**

Triple-nucleoside first-line regimens proved the loss leaders of 2003-2004, with widely noted nosedives by 3TC/ABC/TDF and ddI/3TC/TDF and the failure of Trizivir (TZV, AZT/3TC/ABC) to match EFV-based regimens in AIDS Clinical Trials Group (ACTG) study 5095. While two European cohort studies unveiled in Bangkok saw little difference between three up-front NRTIs and a first-line nonnucleoside regimen, the results looked less than airtight. And a US cohort did much better with an EFV combo than with three nucleosides. Or should NRTI advocates play it safe and use four? Two other studies looked at TZV/TDF as a first or backup regimen.

Lise Cuzin (University Hospital of Toulouse) and colleagues in Nice and Nantes pooled their databases of treatment-naïve people starting either AZT/3TC/ABC or a nonnucleoside regimen after January 1998 [abstract TuPeB4533]. Southern French clinicians evinced symmetrical prescribing sympathies, giving the three Overall virologic failures proved slightly but not significantly higher with AZT/3TC/ABC (5.6 versus 3.7 percent), although the consistently better performance of nonnucleosides from months six through 24 may be persuasive to some. The 36-month analysis rests on follow-up of 95 NNRTI takers and only 39 triple nukers. Intolerance of the two regimens was similar (21 versus 20 percent), and adherence to both regimens was excellent.

Andrew Phillips (Royal Free and University College Medical School, London) and EuroSIDA sidekicks offered a different take on first-line durability, gauging rebound rates among 2,120 people who reined in replication with two NRTIs plus ABC, EFV, NVP, NFV, IDV, or RTV-boosted SQV, IDV, or LPV...
Phillips noted that “this result of these findings with those of ACTG 5095, and EFV had no advantage over ABC. Starting a three-drug first-line regimen, NRTIs than with EFV plus two NRTIs—but only among people who began their triple regimen with single or double nucleoside experience. Among people starting a three-drug first-line regimen, EFV had no advantage over ABC.

Fastidiously wording his comparison of these findings with those of ACTG 5095, Phillips noted that “this result appears to perhaps be inconsistent with a post hoc sub-analysis of ACTG 5095.” However, this statistically savvy and scrupulous researcher added that the confidence interval surrounding the 1.17 rate ratio comparing EFV with ABC was expansive—0.51 to 2.69—“meaning that we cannot exclude the possibility that an appreciable difference in underlying rebound rate does in fact exist.”

Phillip Keiser offered a similar time-to-failure analysis of 653 previously naïve black or Hispanic people treated in Dallas’s Parkland Health and Hospital Systems [abstract TuPeB4540]. Everyone started AZT/3TC plus either ABC, EFV, NVP, or NFV with equivalent group CD4 counts and viral loads. Adherence proved better with ABC and EFV than with NVP or NFV.

In a subanalysis of time to failure among 148 African-American women, EFV did significantly better than ABC or NVP (P = 0.007) and marginally better than NVP (P = 0.13). This finding, Keiser observed, suggests that reported lower EFV levels in African-American women have no clinical cost.

Taken together, results of these three cohort studies do not appear to shake the conclusion of ACTG 5095—a randomized, placebo-controlled trial—that EFV plus AZT/3TC or TZV is a better first-line pick than TZV alone. Would TZV plus TDF do better? A retrospective analysis of 50 treatment-experienced and 25 naive people charted good RNA and CD4 responses to the quadruple regimen and no treatment-limiting toxicities [abstract TuPeB4513].

Parsing records from three HIV clinics in and around New York City, Paola Greiger-Zanlungo (Mt. Vernon Hospital, Mt. Vernon, New York) noted no hypersensitivity reactions, kidney trouble, hematologic toxicity, hypophosphatemia, or grade 3 or 4 side effects of any stripe. No one dropped the quadr regimen because of intolerance, and only one of these 75 people quit for any reason (“patient choice”).

After a median 13 months of follow-up in the 50 people switching to TZV/TDF from a PI or NNRTI regimen, 46 (92 percent) notched a viral load below 400 copies/mL and 38 (76 percent) got under 50 copies/mL. Eleven people (22 percent) had RNA rebounds to high of 1,555 copies/mL at the time of this report. The average CD4 count climbed from 470 to 531 cells/mm3.

The 25 people trying TZV/TDF as their first regimen did even better. After a median 16 months, 21 (84 percent) counted fewer than 400 copies/mL and 18 (72 percent) fewer than 50. The pretreatment CD4 average of 331 cells/mm3 jumped to 597 cells/mm3. Rebounds in four people ranged from 472 to 1,549 copies/mL.

A theoretical advantage of TZV/TDF is that it forces HIV to choose between competitive resistance pathways—the thymidine analog mutation (TAM) route favored by AZT and non-TAM avenues fancied by 3TC, ABC, and TDF. Peter Ruane (Tower Infectious Diseases, Los Angeles) took a closer look at resistance dynamics in people switching to TZV/TDF with an undetectable load or one below 10,000 copies/mL and genotypic evidence of a dominant or archived M184V 3TC mutation with or without one to two TAMs (M41L, D67N, K70R, L210W, T215Y/F, T215S/C).

### Table 9. Lower risk of failure with EFV in 653 African Americans and Hispanics

<table>
<thead>
<tr>
<th>Drug (vs abacavir)</th>
<th>Risk of failure</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>0.49</td>
<td>0.33 to 0.71</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>0.93</td>
<td>0.68 to 1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>0.99</td>
<td>0.61 to 1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Other variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>0.92</td>
<td>0.70 to 1.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Male</td>
<td>0.97</td>
<td>0.72 to 1.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Baseline CD4 &lt;200 cells/mm³</td>
<td>0.98</td>
<td>0.74 to 1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Baseline RNA &gt;100,000 copies/mL</td>
<td>1.8</td>
<td>1.4 to 2.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Percent adherence</td>
<td>0.26</td>
<td>1.7 to 0.38</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Source: Phillip Keiser, abstract TuPeB4540.
K219Q/E) [abstract TuPeB4600]. No one had the TDF- or ABC-linked K65R or L74V mutation, and no one had taken either of those drugs.

The 20 people who met those criteria had tried a median of 5.5 regimens including a median of four NRTIs. Ruane counted only three people (15 percent) in whom TZV/TDF failed to achieve or maintain a viral load below 75 copies/mL, all of whom had multiple mutations at baseline (M184V plus TAMs with or without NNRtI or PI mutations). The best responders started TZV/TDF with only M184V, including people who started therapy with only 3TC plus AZT or d4T. Lipid profiles improved in most responders.

**High maintenance**

Results of three small, brief induction-maintenance studies suggest LPV/RTV mono-maintenance has yet to prove itself as safe as continued triple therapy (see “Only Kaletra OK?” above). In the one randomized study in the group [abstract TuPeB4486], no one in the control arm met the study definition of failure, while four in the LPV/RTV monotherapy arm did. Three other Bangkok studies—two of them randomized—weighed the merits of different induction-maintenance strategies, with equally inconclusive results. (See “Quest” below for an induction-maintenance study starting with SQV/RTV.)

Martin Markowitz (Aaron Diamond AIDS Research Center, New York) and colleagues from other sites sized up TZV-only maintenance versus continued TZV/EFV and found equivalent responses in the two arms [abstract LbOr14]. But they noted more virologic washouts with TZV-only maintenance, and the 96-week study suffered from a high dropout rate.

The trial started with 448 treatment-naive people taking both EFV and TZV (AZT/3TC/ABC). Markowitz aimed to randomize those with a 48-week sub-50-copy load to stick with the four drugs or to scale back to TZV alone. Although a discouraging 37 percent dropped out before week 48, the remaining 228 satisfied protocol requirements for a 96-week comparison.

The 96-week missing-data-equal failure analysis rated the maintenance arms equivalent, with 79 percent on TZV and 77 percent on TZV/EFV under 50 copies/mL. More than twice as many people who trimmed back to TZV alone had a virologic failure (seven versus three, or 4.9 versus 2.1 percent), but that difference lacked statistical significance. While 89 percent of TZV-only maintainers reported complete adherence, 80 percent on TZV/EFV said they took all their pills ($P = 0.057$). Two in the TZV-only arm and four taking four drugs quit the maintenance phase because of side effects. The TZV/EFV group also had more dropouts for “other” reasons (six versus two), and researchers attributed five TZV/EFV dropouts to nonadherence.

Markowitz regretted the high dropout rate in the induction phase, saying it complicated interpretation of the maintenance results. Still, he believes the trial shows the validity of induction-maintenance.

AIDS Research Center, New York) and colleagues from other sites sized up TZV-only maintenance, and the 96-week study suffered from a high dropout rate. The Gasthuis gang tracked 42 untreated people who started AZT/3TC/ABC plus LPV/RTV, striving to stifle replication below a 50-copy quotient. They began the four-drug mix with a median viral load of 181,377 copies/mL and a median 180 CD4 cells/mm$^3$. Two people had yet to break the 50-copy threshold at the time of this report, and 10 (24 percent) quit the induction phase with side effects.

Of the 30 people who shelved LPV/RTV with a sub-50 load, 26 (87 percent) continued to harness HIV for an average 54 weeks (range five to 98 weeks). Two of the four failures—one attributed to poor adherence—came with the 3TC-induced M184V mutation. One person stopped TZV with a “suspicion” of hypersensitivity to ABC after taking the triple drug for 12 months, and one stopped with fatigue. In a strict intent-to-treat analysis, van Raalte figured a 62 percent success rate (26 of 42 people) after a mean 54 weeks of follow-up.

A multicenter French group headed by Pierre-Marie Girard (Saint-Antoine Hospital, Paris) offered findings from the still-blinded COOL trial, which randomizes people to once-daily maintenance with 3TC/TDF/EFV or TDF/EFV [abstract TuPeB4493]. Enrollees must be taking a stable regimen for three or more months and must have no treatment failures on their charts. Although another entry criterion is a viral load below 50 copies/mL, baseline RNA readings ranged from 20 to 88 copies/mL. Starting CD4 counts went from an eyebrow-arching 78 cells/mm$^3$ to 1,775 cells/mm$^3$.

Girard registered nine blips above 50 copies/mL through 24 weeks of follow-up and one confirmed rebound in 44 people tested so far. Which regimen that rebounder took remains unknown since blinding continues. The Data Safety and Monitoring Board (DSMB) met once so far and advised continuing the trial.

**Salves**

Salvage salvage did not go ignored in Bangkok, where four groups tendered tentative rescue strategies. Hartmut Stocker (Vivantes Augusta-Victoria-Klinikum, Berlin) advanced Hypothesis 1.

--- HYPOTHESIS (1) ---

*Regular switches between two regimens— one targeting protease only and one only reverse transcriptase—will continuously lower viral load and raise CD4 counts.*

A similar concept got an earlier airing at the XIV International AIDS Conference in 2002, where Franco Maggiolo (Ospedali Riuniti, Bergamo, Italy) proposed a scheme called “strategic selective pressure”—genotyping people with multidrug-resistant virus and a viral load above 10,000 copies/mL every two months, then switching to drugs most likely to counter the prevailing resistant population.

Stocker’s approach involved switching only between NRTIs and PIs. He recruited 15 people, excluding anyone with virus sensitive to more than two antiretrovirals [abstract TuPeB4556]. They began at least three nucleosides, then switched to two PIs (plus an RTV boost) when their viral load rose more than a half log. When the viral load rebounded a half log on the PI regimen, they switched back to three or more NRTIs.

Twelve people in Stocker’s pilot study completed 48 weeks of flip-flop therapy. The mean viral load dipped 0.22 log (95 percent CI +0.46 to -0.45 log), while the average CD4 count remained unchanged. From 30 to 60 percent of study
participants—depending on cycle and baseline CD4 count—saw more than a 1-log viral load drop with each drug switch. People with more than 200 CD4 cells/mm³ before taking antiretrovirals enjoyed the biggest viral load drops.

During NRTI therapy genotyping confirmed the partial loss of circulating PI mutations, while the shift to double boosted PIs prompted the hasty retreat of NRTI mutations, especially M184V. Stocker concluded that viral resensitization is feasible with this strategy and that people with multidrug-resistant virus can remain stable clinically and virologically. Longer and more detailed follow-up in more people will merit scrutiny.

Victoria Latham (St. Stephen’s AIDS Trust, London) explored just the NRTI side of Stocker’s salvage seesaw—quadruple therapy with TZV and TDF [abstract TuPeB4554]. She based her study on Hypothesis 2.

- HYPOTHESIS (2) -
Treatment simplification may improve adherence in people in whom successive regimens have failed; this may lead to renewed virologic success.

To test this theory, Latham took a retrospective look at everyone in the database taking TZV/TDF after failure of at least one regimen. The 122 people identified had tried an average four combinations and had a mean CD4 count of 221 cells/mm³; 87 percent had taken 3TC (mean 22 months), 77 percent AZT (mean 15 months), 55 percent ABC (mean 12 months), and 26 percent TDF (mean two months).

Forty-nine people (40 percent) quit tetranaque therapy within a year, but only 15 (12 percent) because of virologic failure, and no new mutations emerged in these people. Fourteen stopped with side effects, 14 stopped keeping appointments, two switched after disease progression, and five quit for other reasons.

Among 63 people who stuck with TZV/TDF for one year, 41 (65 percent) had a viral load under 50 copies/mL. The number of already used drugs in the regimen, treatment with any one of the four drugs, and the 3TC-inspired M184V mutation did not influence virologic outcome. Numbers of thymidine analog mutations (TAMs) did. Viral loads dropped below 50 copies/mL in 38 percent who started TZV/TDF with one or no TAMs and in 17 percent who started with two or more (P = 0.03). One of three people who began salvage with the TDF-triggered K65R mutation had a virologic failure.

Using mean cell volume (an AZT token) as a rough-and-ready adherence guide, Latham found that significantly more people with a volume above 100 fl reached a sub-50 load than did those with a volume below 100 fl (P = 0.04) after four months of therapy. Total cholesterol fell 0.5 mmol/L in six months.

One reason this regimen did well in people with lots of AZT and 3TC experience, Latham offered, is that M184V resensitizes virus to AZT. At the same time, M184V mutants are less fit than nonmutant virus. These verities pointed Antonella Castagna (San Raffaele University, Milan) to Hypothesis 3.

- HYPOTHESIS (3) -
Maintaining the M184V mutation by sustained drug pressure may delay immunologic failure.

This ongoing pilot study randomized 50 people with a viral load above 1,000 copies/mL and a CD4 count topping 500 cells/mm³ while taking a 3TC regimen to stop all drugs or continue only 3TC at a dose of 300 mg once daily [abstract WeOrB1286]. Median CD4s stood at 629 cells/mm³ in the drug break group and 620 cells/mm³ in the 3TC monotherapy group, while respective nadirs lay at 260 and 283 cells/mm³. The median viral load and years of therapy were 3.78 logs and 6.7 years for the interrupters and 3.91 logs and 7.1 years for the 3TC takers. Both groups had tried a median of two PIs and one NNRTI. No one with HBV infection or an active opportunist could enter the study.

Defining failure as a CD4 count below 350 cells/mm³ or a new HIV-related diagnosis, Castagna counted 14 failures (including one withdrawn consent) in the treatment break group (56 percent) and seven (28 percent) in the 3TC group after 24 weeks of follow-up. The average CD4 count slipped 153 cells/mm³ among interrupters and 73 cells/mm³ with 3TC. Respective viral loads flared 1.2 logs in the drug holiday group and 0.6 log with mono 3TC. Among 23 break takers genotyped at week 24, the M184V mutation had dipped below detection thresholds in 17 (74 percent) but in none of 20 who kept taking 3TC.

Again, whether this strategy can stand as a useful stopgap awaits further follow-up, but it seems to do no harm in closely monitored people. However, research presented earlier this year showed no virologic advantage to continuing versus stopping 3TC in a rescue regimen after a 3TC-containing regimen failed. That result suggests that keeping M184V in the foreground has little or no virologic benefit after failure.

Because LPV/RTV retains activity against some PI-resistant virus, Daniel Podzamczer (Hospital Universitari de Belvitge, Barcelona) and coworkers from other sites broached Hypothesis 4.

- HYPOTHESIS (4) -
Higher than standard doses of LPV/RTV may boost LPV levels high enough to overcome some degree of reduced susceptibility to the PI and so prove therapeutically profitable.

Recruiting 36 people with RNA readouts above 1,000 copies/mL, treatment with one or more drugs from the PI and reverse transcriptase classes, and a steady regimen for eight weeks or more, Podzamczer assigned 17 people to 400/300 mg of LPV/RTV twice daily and 19 to 667/167 mg twice daily plus three or more NRTIs but no NNRTIs [abstract TuPeB4555]. The median baseline load stood at 4.7 logs (range 3.21 to 5.88 logs) and the median CD4 count at 96 cells/mm³ (range 2 to 642 cells/mm³). PI experience ranged from one to five drugs with a median of four.

The two regimens yielded similar LPV troughs 60 to 70 percent higher than scores with standard-dose LPV/RTV. The 400/300-mg dose upped RTV exposure about six-fold above standard levels, while the 667/167-mg draught doubled RTV exposure. The median LPV inhibitory quotient (IQ = LPV baseline trough/fold change in susceptibility to LPV) measured 27 and ranged from 0.7 to 438.

Multivariate machinations independently linked higher LPV IQ, more active NRTIs in the regimen, and a lower baseline RNA with a viral load below 400 copies/mL at 48 weeks. More people taking 400/300 mg than 667/167 mg had a viral load above 400 copies/mL at that point, though average viral load drops in the two groups were similar (Table 10). The 400/300-mg group did worse than the 667/167-mg
group in side effect measures, but adherence was better with 400/300 mg (Table 10).

Grade 3 or 4 lipid elevations proved significantly more common with 400/300 mg than with 667/177 mg at week 48 (P = 0.02). Median total cholesterol rose 97 mg/dL and triglycerides 41 mg/dL with 400/300 mg and fell 5 mg/dL and 1 mg/dL with 667/167 mg. All told, Podzamczer concluded that 667/167 mg twice daily is more tolerable than 400/300 mg twice daily.

**STIs**

Because the rationale behind structured treatment interruptions (STIs) has changed, they probably need a new name. When these planned interludes in treatment (PI Ts?) first galvanized the group-think of treatment-weary masses, all hoped this take-a-break scheme (TABS?) would crank up immune moxie or wash out noxious mutants enough to help control HIV. Evidence affirming these notions remains scant and pendent. So treatment break theorists made a midcourse correction, espousing patterned antiretroviral layoffs (PALS!) guided by CD4 counts or viral loads as a way to limit toxicity and drug fatigue.

Calvin Cohen (CRI New England, Boston) developed his own acronym, FOTO, to describe a five-day-on-two-day-off plan for people with sustained viral suppression [abstract TuPeB4575]. He signed up 30 people taking two or three NRTIs plus EFV, NVP, or a PI. When poised to start FOTO, the group sported a median CD4 count of 542 cells/mm³ (range 221 to 1,162 cells/mm³) and a median RNA load below 50 copies/mL (range <50 to 516 copies/mL).

Cohen’s FOTO formula worked in 24 of 26 people who completed at least 24 weeks of weekend holidays. Ten of 10 people taking EFV and seven of seven taking NVP kept their viral load below 50 copies/mL through week 24, but two of nine PI takers had confirmed rebounds above 500 copies/mL. All seven PI-treated people who maintained a sub-50 load for the first 24 weeks did so for another 24. Both rebounders in the PI group regained viral control when they resumed daily therapy. CD4 counts stayed stable through the 48-week FOTO finish in everyone.

Cohen had three dropouts not related to study drugs, and he recorded no serious toxicity. Nine people did report side effects after two-day breaks from EFV (n=4), NVP (n=1), or a PI (n=4), a worrisome trend for people not completely committed to cyclic on-off switches. But self-reported adherence measured 100 percent in Cohen’s study.

Before legions line up for their own FOTO opportunity, Cohen cautioned that his study is small and nonrandomized, the implications of rebounds in the PI group are uncertain, and the strategy’s impact on long-term complications remains unclear. Fasting lipids did not improve through 48 weeks of follow-up. Indeed, mean triglycerides inched upwards. Cohen also observed that no one knows how five-on-two-off therapy may affect adherence to other drugs or interactions with non-antiretrovirals.

Cohen’s five-day-two-day plan worked better than the week-on-off strategy tried by one of three groups in the Staccato study [abstract WeOrB1283]. That arm had to be shut down early, reported Jintanat Ananworanich (HIV-NAT, Bangkok), when researchers saw a rash of virologic breakthroughs. This unhappy result offers a blunt reminder that two small pilots of a novel tactic37,38 do not make a standard of care.

The HIV-NAT team enrolled 74 Thais with dual-nucleoside experience who then took SQV/RTV (1,600/100 mg once daily) plus AZT/3TC or ddI/d4T for three years. People with a viral load below 50 copies/mL and a CD4 count above 350 cells/mm³ got randomized to continuous therapy, a week-on-week-off STI, or an STI guided by a 350-cell/mm³ threshold or a 30 percent CD4 drop or rise. Pretreatment and pre-HAART viral loads were significantly lower in the continuous therapy group (4.3 and 2.6 logs) than in the CD4-guided group (4.8 and 3.2 logs) or the week-on-week-off group (4.9 and 3.4 logs) (P < 0.05).

Jintanat and colleagues closed the week-on-week-off arm at week 72 after 13 of 26 people met with virologic failure (more than 500 copies/mL). Among the 13 failures, four of eight people genotyped had resistance mutations; three rekindled NRTI mutations from their double-nuke days, while one had a new mutation in protease. Everyone in that group resumed continuous therapy and put HIV back in check. At 72 weeks, none of 25 in the continuous arm and one of 23 in the CD4-guided arm had a virologic failure.

After 108 weeks, everyone in the steady-HAART group still had a viral load under 400 copies/mL and 24 had a sub-50 load. Twenty-one of 22 in the CD4-guided group had a load under 400 copies/mL at 108 weeks, but only 13 (59 percent) sat below the 50-copy line (P = 0.003). Among 18 break takers with 120 weeks of follow-up, however, all but one had a sub-50 load, and that person had poor adherence. Twenty-four of 25 in the continuous arm had a week 120 load below 50 copies/mL. Archived NRTI
mutations did not correlate with virologic response in these two groups [abstract TuPeB4562]. CD4 tallies proved significantly lower with CD4-guided STIs (488 cells/mm³) than with continuous therapy (661 cells/mm³) ($P < 0.05$).

Compared with steady treatment, the CD4-steered STI did not improve lipids or quality of life. Despite the higher 108-week failure rate and lack of lipid or life quality benefit, Jintanat argued that CD4-guided therapy makes sense for antiretroviral-poor countries because it saves so much money—46 percent of drug costs in this trial. And the heightened monitoring needs of CD4-adjusted therapy did not wipe out these savings. Whether the same argument can be made in places with easy access to antiretrovirals is another question. Shaky adherence may have caused the one 120-week failure in the STI arm, but stopping and starting drugs every time T cells wane may have caused the one 120-week failure in the STI arm, but stopping and starting drugs every time T cells wane could abet bad adherence. Lídia Ruiz ( Germans Trias i Pujol University Hospital, Barcelona) used both CD4 count and viral load to guide drug breaks in 100 people taking a potent regimen for at least a year [abstract TuPeB4567]. All had a viral load below 400 copies/mL for at least a year and below 50 copies/mL at screening. People restarted treatment if their CD4s slid under 350 copies/mL at screening. People restarted for more than one year and below 50 copies/mL. All had a viral load below 400 copies/mL for at least a year [abstract TuPeB4567].

The 47 volunteers had a CD4 count above 500 cells/mm³ and a viral load under 200 copies/mL at 50 copies/mL when taking their first antiretrovirals. The ACTG team randomized them to continue their current regimen or add three cycles of interleukin 2 (IL-2) at a dose of 4.5 million units subcutaneously twice daily for five days every eight weeks. The pretreatment CD4 count measured 344 cells/mm³ for the whole group, and the pretreatment viral load 4.41 logs.

When the STI started the 23 IL-2-treated people had a median CD4 count of 1,331 cells/mm³ compared with 757 cells/mm³ in the 24 people not taking IL-2. That CD4 edge kept more people in the IL-2 group above the 350-cell restart trigger through 24 weeks, but after 48 weeks similar numbers in both groups had to resume therapy. Still, 28 people overall (60 percent) managed to keep their antiretrovirals under lock for 48 weeks. Two people endured retroviral syndrome throes when they had to restart therapy.

As in other STI studies, a lower nadir CD4 count, lower count at STI, and higher pre-HAART viral load favored a shorter time to resumed therapy. A briefer time to the viral load set point during the STI (14 versus 23 weeks) also correlated with earlier retreatment.

Analysis of 140 people who suspended therapy when they had more than 500 CD4 cells/mm³ also showed a shorter time to retreatment in people with lower CD4 nadirs [abstract TuPeB4569]. Restarting therapy whenever CD4s sagged below 350 cells/mm³ or when the study participant wanted to, Cristina Mussini (Clinic of Infectious Diseases, Milan) logged an off-treatment median of 52 weeks in those with a sub-350 nadir versus 154 weeks in those with a higher nadir ($P = 0.01$). She spotted four independent predictors of a drop below 350 cells/mm³:

- CD4 nadir per 100 cells higher: relative hazard (RH) 0.74, 95 percent CI 0.55 to 0.99, $P = 0.04$
- >12 months with RNA <50 copies/mL: RH 0.16, 95 percent CI 0.06 to 0.42, $P = 0.0002$
- Slope of pretreatment CD4 drop per cell per month faster: RH 1.26, 95 percent CI 1.02 to 1.54, $P = 0.04$
- Most recent RNA versus RNA at STI per log higher: RH 1.54, 95 percent CI 1.01 to 2.35, $P = 0.04$

Mussini did not report the emergence of any mutations during drug breaks.

Early results from a randomized study by Alejandro Krolewiecki (Fundación Huésped, Buenos Aires) suggest that most people with CD4 nadirs down to 250 cells/mm³ can safely stay off therapy for 48 weeks, if the restart signal is 250 cells/mm³ on two visits or a 1-log leap in viral load on two visits [TuPeB4584]. Only one of 39 people had to resume treatment.

If structured drug breaks have their
risks, unstructured breaks have more. Tracking disease markers and clinical progression in 1,062 ATHENA cohort members who suspended HAART and 1,062 matched controls who did not, Ard van Sighem (Academic Medical Center, Amsterdam) charted a 2.7 times higher risk of a new CDC class C diagnosis in people who put therapy on hold (95 percent CI 2.0 to 3.6). Progression risk was higher in people with a lower CD4 count, a viral load above 100,000 copies/mL, or an AIDS diagnosis before HAART. In the drug holiday group, 19 percent failed to get their viral load back under 500 copies/mL within 12 months of resuming treatment.

### Table 11. Comparison of five HAART intervention scenarios in South Africa

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Current WHO criteria</th>
<th>Previous WHO criteria</th>
<th>All symptomatic disease</th>
<th>AIDS only</th>
<th>&lt;200 CD4 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible for HAART (%)</td>
<td>552 (56.7)</td>
<td>487 (50)</td>
<td>433 (44.5)</td>
<td>126 (12.9)</td>
<td>447 (45.9)</td>
</tr>
<tr>
<td>Death rate without HAART</td>
<td>36.6</td>
<td>37.5</td>
<td>48.6</td>
<td>81.2</td>
<td>35.2</td>
</tr>
<tr>
<td>Death rate with HAART</td>
<td>6.5</td>
<td>8.3</td>
<td>7.4</td>
<td>14.1</td>
<td>8.9</td>
</tr>
<tr>
<td>Relative risk of death</td>
<td>0.18</td>
<td>0.23</td>
<td>0.16</td>
<td>1.10</td>
<td>1.16</td>
</tr>
<tr>
<td>Deaths averted</td>
<td>30.0</td>
<td>28.9</td>
<td>40.8</td>
<td>74.0</td>
<td>24.6</td>
</tr>
</tbody>
</table>

* Current WHO criteria: stage 4 disease (AIDS), stage 3 and CD4s <350 cells/mm³, stage 1, 2, or 3 and CD4s <200 cells/mm³
* Previous WHO criteria: stage 4 (AIDS), stages 1, 2, and 3 and CD4s <200 cells/mm³; all symptomatic disease: stage 3 and 4 disease; AIDS only: stage 4 disease.

1. Current WHO criteria: stage 4 disease (AIDS), stage 3 and CD4s <350 cells/mm³, stage 1, 2, or 3 and CD4s <200 cells/mm³
2. Previous WHO criteria: stage 4 (AIDS), stages 1, 2, and 3 and CD4s <200 cells/mm³
3. All symptomatic people (stages 3 and 4)
4. Stage 4 (AIDS) only
5. CD4s <200 cells/mm³

Their revealing conclusion—hewing to revised WHO guidelines would get more people into treatment (P < 0.05) but would prevent fewer deaths than simply treating people with symptomatic (stage 3 or 4) disease (Table 11). At the same time, cost-effectiveness analyses showed that treating people with symptomatic disease yielded more life years or quality-adjusted life years at a lower cost than not treating them. Cost-effectiveness ratios indicated that beginning HAART in stage 3 disease ends up saving more money than waiting to treat stage 4 disease.

**Best**

A spidery web of fortune and fortuity yielded the world’s favorite fixed-dose triple combination: d4T, 3TC, and NVP, variously dubbed Triomune (Cipla), Triviro (Ranbaxy), GPO-VIR (Thai Government Pharmaceutical Organization), Nevilast (Genexpharma), and Stavex (Aurobindo). But is it the best triple therapy? Or even a strong contender?

The WHO’s guideline givers anointed NVP or EFV plus AZT/3TC or d4T/3TC as the first-line favorite. The latest US Department of Health and Human Services brain trust opts for EFV/3TC plus AZT, TDF, or d4T or LPV/RTV/3TC plus AZT or d4T, but not NVP. The British HIV Association (BHIVA) likes first-line EFV or NVP but booted d4T from its up-front favorite list. So only the WHO sanctions starting with d4T/3TC/NVP, although they had to consider factors not relevant to rich countries.

To rate the first-line muscle of d4T/3TC/NVP, Thira Woratanarat (Johns Hopkins University, Baltimore) scoured the literature for studies of this regimen in treatment-naïve people and found only five from the past 10 years. Three were prospective trials and only one randomized (see note 48). That trial involved 52 people and ran for 52 weeks, after which 71 percent had a viral load under 500 copies/mL. One in four enrollees stopped coming back for visits before the trial ended, and 23 percent had drug-related grade 3 or 4 side effects.

The other two prospective studies enrolled 25 and 26 naïve people and ran 12 and 31 months. In the first of these two, 28 percent dropped out and 90 percent of those left reaped a 12-month load below 400 copies/mL. The third prospective study was a community-based program that ran for 31 months and had “ambiguous results.”

The two retrospective studies scanned records of 54 and 73 people treated with d4T, 3TC, and NVP for 12 months. Although the 400-copy response rate ranged from 72 percent to 80 percent, an astonishing 75 percent stopped coming back for checkups during the year.

Thira concluded that although the virologic response to d4T, 3TC, and NVP generally looks good, that conclusion rests on studies with small populations, high dropout rates, and brief follow-up.

**WHO knows?**

To test WHO treatment guidelines, Badri compared time to AIDS or death in 292 adults enrolled in HAART clinical trials and 974 untreated adults attending a South African hospital between 1992 and 2001. Badri projected the number of people who would be eligible for HAART and resulting deaths averted according to five treatment criteria:

1. Current WHO criteria: stage 4 disease (AIDS), stage 3 and CD4s <350 cells/mm³, stage 1, 2, or 3 and CD4s <200 cells/mm³
2. Previous WHO criteria: stage 4 (AIDS), stages 1, 2, and 3 and CD4s <200 cells/mm³
3. All symptomatic people (stages 3 and 4)
4. Stage 4 (AIDS) only
5. CD4s <200 cells/mm³

### ANTIRETROVIRAL STRATEGIES

(South/East)

Strategy studies from developing countries typically reflect three desiderata:

- The drugs in hand
- How they can be used
- How they must be used

Generic drug makers, generous funders, policy pooh-bahs, and sometimes even physicians mold these pivotal priorities, interpreting a slurry of trial trends, patent arcana, market markers, and mortality rates, and partly responding to guidelines proposed by the WHO, whose expert panel advises treating anyone with AIDS; WHO stage 1, 2, or 3 HIV disease; and a CD4 count below 200 cells/mm³, or WHO stage 3 disease with a CD4 count between 200 and 350 cells/mm³. But in sub-Saharan Africa nearly one third of people with fewer than 200 CD4 cells/mm³ have stage 3 disease, according to Motasim Badri (University of Cape Town) [abstract TuPeB4515]. So Badri and colleagues at the Desmond Tutu HIV Centre asked how practical WHO guidelines are in Africa’s AIDS epicenter.
Countries relying on this regimen, he worried, may quickly find the need for a more expensive rescue regimen.

Sanny Chen (Johns Hopkins University, Baltimore) offered another perspective on the relative merits of first-line regimens by reckoning survival odds among 1,471 San Franciscans with AIDS who started a combination containing at least one NNRTI or one PI as their first regimen [abstract MoOrC1082]. She matched cases (those who died before 2003) with controls (those still alive by 2003) for year of HIV diagnosis and year and level of earliest recorded CD4 count.

A multivariate analysis adjusted for age, injecting drug use status, homelessness, race, and CD4 count before treatment determined that people who started an NNRTI plus two NRTIs had a 41 percent lower risk of death than people who started a PI plus two NRTIs. But that analysis says little about contemporary options because it included only a smattering of boosted PIs. Chen’s more important finding may be the significantly lower risk of death with d4T/3TC/EFV than with any other regimen, including d4T/3TC/NVP ($P = 0.02$).

Bangkok’s HIV-NAT crew found that d4T/3TC/NVP has little to offer after double-nucleoside failure [abstract TuOrB1192]. Jintanat Ananworanich offered a cross-sectional analysis of 100 Thai children treated with dual NRTIs for more than six months in HIV-NAT 013. Most took AZT/ddI (68.4 percent) or AZT/3TC (18.9 percent). Only a handful had tried ddI/d4T (6.3 percent) or d4T/3TC (5.3 percent). But resistance results indicated that the Thai version of d4T/3TC/NVP (GPO-VIR) would not work as rescue therapy because of the heavy burden of thymidine analog mutations (TAMs), a legacy of heavy AZT use.

Almost all the children—96.8 percent—had at least one NRTI mutation, and 89.5 percent had TAMs. Forty percent had four or more TAMs, and another 31.6 percent had the M184V mutation conferring resistance to 3TC. Cross-resistance between AZT and d4T in these children measured 99 percent.

Jintanat concluded that d4T/3TC/NVP would be a risky choice in this group since most children had virus already resistant to d4T or 3TC. She urged colleagues in other countries to avoid beginning therapy with two nucleosides. For people already taking two nukes, she suggested that clinicians consider deferring rescue therapy until immunologic failure.

Mark Boyd, another member of Bangkok’s HIV-NAT team, reported that twice-daily IDV/RTV (800/100 mg) plus 600 mg of EFV once daily added up to a potent rescue regimen for 38 men and 23 women who started their antiretroviral pilgrimage with two nucleosides [abstract MoOrB1084]. After 96 weeks of treatment, an intent-to-treat analysis found 68.8 percent with a viral load under 50 copies/mL and 82.4 percent under the 50-copy mark in an on-treatment analysis.

Five people quit because of virologic failure and five for other reasons. Although 24 (39 percent) endured serious side effects, only two stopped the NRTI-sparing regimen because of toxicity. This PI/NRTI mix proved hard on lab markers, significantly boosting triglycerides and glucose. But the total-to-HDL cholesterol ratio, hemoglobin, and alanine aminotransferase levels all improved significantly. Of course the rate-limiting factor for this regimen in developing countries is not toxicity, but availability.

**Quest**

As Mark Boyd’s study (above) shows, the still-stressed antiretroviral supply lines to much of Asia, Africa, and Latin America have not stopped researchers in poor and middle-income countries from a quest for more adventurous remedies. Perhaps the most compelling STI results from the conference, the week-on-week-off strikeout in Staccato (see “STIs” above), involved people from Thailand. And the still-blind-ed Trivacan STI trial in the Ivory Coast is comparing continuous therapy with two-months-off-four-months-on and CD4-guided treatment breaks [abstract WeOrB1284].

Although CD4-guided STIs seem safe in settings with reliable monitoring—an HIV-NAT trial, for example—they could prove a high-wire escapead in other places, especially where taxed healthcare workers have little time to explain what may seem a random treatment timetable to poorly educated people inclined to share their drugs with others. Staccato showed that CD4-directed dosing can save plenty of money and so, in theory, get drugs to more people who need them. But theory does not invariably square up with practice, and science has yet to show that years of off-and-on therapy have no downside. How will regular drug holidays affect adherence? Viral reservoir reseeding? HIV-specific CD4 quotients?

Finally, one mustn’t forget that trials themselves can be dangerous. Plenty of STI study volunteers ended up with resistant virus they may not have had, absent the hand of bold research. Drug-resistant HIV seems primed to appear in Trivacan, for example, with 88 percent of enrollees taking AZT/3TC/EFV and continuing the AZT/3TC for only five days after stopping EFV. The languid clearance of this nonnucleoside practically guarantees that many study volunteers (75 percent of them women) will be taking EFV monotherapy for more than a few days. Ethics panels must exercise unstinting stringency to ensure that people with little support and less learning are not asked to sacrifice their wild-type virus (never mention their lives) in over-intrepid or under-planned trials.

Even the still highly speculative tactic of boosted PI monotherapy (see “Only Kaletra OK?” above) has made inroads south of the Sahara. Reasoning that people sick with HIV have problems NRTIs or NNRTIs can provoke—anemia, neutropenia, stressed livers—Osman Ebrahim (Brenthurst Clinic, Johannesburg) tried 600/100 mg of SQV/RTV twice daily in 15 men and 13 women with no antiretroviral experience, planning to switch later to an all-RTI regimen [abstract TuPeB4492]. (The usual SQV/RTV dose is 1,000/100 mg twice daily or 1,600/100 mg once daily; these volunteers weighed less than most Westerners.)

With a mean age of 33 years (range 20 to 55 years) and mean weight of 59.5 kg (range 35 to 68 kg), study participants began RTV-boosted soft-gel SQV while averaging 26 CD4 cells/mm$^3$ (range 7 to 110 cells/mm$^3$) and 5.5 log copies/mL of HIV RNA (range 4.6 to 6.6 logs). Weakness, bloating, and diarrhea slowed some people in the first two weeks of treatment, but all 28 finished eight weeks of SQV/RTV induction. Everyone enjoyed CD4 gains and better viral control, while certain morbidity markers improved (Table 12).

Nearly two years after their HIV diagnosis, and after switching to a standard NRTI/NNRTI combination, 26 of these 28 people are well and active. Disseminated Mycobacterium avium infection struck
two people; one died and the other is critically ill. Whether this mono-PI ploy holds any advantage over starting an NNRTI regimen and monitoring closely or starting a boosted PI with tolerable NRTIs—when available—remains to be tested.

Grandmothers

No developing world antiretroviral plan holds greater urgency while posing graver ethical questions than preventing mother-to-child transmission (MTCT). Fond hopes that single-dose NVP for mother and neonate would stanch transmission cheaply and safely turned sour when this triple irony arose:

- A single NVP dose readily breeds resistance in a woman with uncontrolled viremia.
- NVP-resistant virus lasts and lasts.
- Fixed-dose generic formulations to treat women after delivery often feature NVP as their crux.

But research by James McIntyre (University of Witwatersrand, Johannesburg) may point a way out of this awful moral bind [abstract LbOrB09]. His randomized study of 61 pregnant women and their newborns showed that a brief course of AZT/3TC — available as a generic agent — greatly limits emergence of resistance to AZT/3TC — available as a generic agent — greatly limits emergence of resistance to AZT or 3TC emerged. With these results in hand, the researchers closed the standard short-course NVP arm and continue to compare the four- and seven-day CBV add-ons.

These early results do not pave a painless escape route from MTCT-related resistance. The 3TC-evoked M184V mutation could evolve in women or neonates treated this way, and M184V would also undercut the favored generic triple, d4T/3TC/NVP, and so threaten fast emergence of NVP-linked mutations. But the findings do suggest that short-course NVP should not be tossed into the overfull dustbin of this epidemic’s disappointments.

McIntyre sought to defuse the highly charged Bangkok conference debate over this strategy by urging that “we must be very responsible in what we say about NVP [for mother-to-child transmission]—because we don’t have many options.” Policy makers, politicians, and self-appointed pundits who don’t look after infected women and their too-often infected offspring might listen first to those who do.

The world could make this moral issue moot by implementing a measure eminently within its grasp: treating all infected pregnant women with potent antiretrovirals. An undetectable viral load would not totally thwart HIV transmission, but it would make the risk as negligible as it is in treated European and American women. And higher maternal loads independently lift the risk of death in infected infants, according to results of a prospective observational study by Elizabeth Obimbo (University of Nairobi) [abstract TuOrB1187].

Preliminary analysis showed that nine of 18 women (50 percent) taking only NVP had resistance mutations within six weeks of delivery compared with one of 20 (5 percent) in the four-day CBV group and three of 23 (13 percent) in the seven-day CBV group. No mutations compromising AZT or 3TC emerged. With these results in hand, the researchers closed the standard short-course NVP arm and continue to compare the four- and seven-day CBV add-ons.

This research involved 79 infants infected with HIV despite short-course AZT prophylaxis in 63 (80 percent) of their mothers. Higher maternal viral loads meant higher loads in their children ($P = 0.001$) and higher infant mortality. Whereas 20 percent of infants born to women with loads below 10,000 copies/mL died before age two years, 24 percent whose mothers had 10,000 to 100,000 copies/mL died, and 65 percent whose mothers had more than 100,000 copies/mL died. A multivariate analysis tied three factors to infant death:

- Viral load during pregnancy (per log higher): hazard ratio (HR) 2.2, $P = 0.02$
- Infant peak load (per log higher): hazard ratio (HR) 1.6, $P = 0.07$
- Birth weight below 2.5 kg: HR 4.5, $P = 0.002$

What can be done to impede HIV transmission if a new mother breastfeeding a child born without the virus? Two Bangkok studies suggested divergent options: Give them TDF, or give them grandmothers. The TDF trial involved infant monkeys exposed to a highly virulent simian immunodeficiency virus (SIV) in three daily bottle feedings for five straight days in the first week of life, then again a month later if they remained uninfected [abstract LbOrB10]. Control animals got no TDF, while six monkeys got 10 mg/kg

<table>
<thead>
<tr>
<th>Table 12. First-line SQV/RTV monotherapy for advanced disease</th>
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<tbody>
<tr>
<td>Median improvement at weeks 4 to 8 (n = 28)</td>
</tr>
<tr>
<td>CD4 cells/mm$^3$ (range)</td>
</tr>
<tr>
<td>HIV RNA log copies/mL (range)</td>
</tr>
<tr>
<td>Hemoglobin (% change in median)</td>
</tr>
<tr>
<td>Neutrophils (% change in median)</td>
</tr>
<tr>
<td>AST (% change in median)</td>
</tr>
<tr>
<td>ALT (% change in median)</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Source: Osman Ebrahim, abstract TuPeB4492.
of TDF from one day before to one day after SIV exposure. Koen van Rompay (University of California, Davis) picked this dose as the pharmacokinetic equivalent of the 8 mg/kg used in human pediatric trials.

Twenty-four of 26 exposed but untreated macaques wound up with SIV infection. The virus took hold in one of six treated monkeys after the first round of SIV exposure and in another two after the second round. The total 50 percent transmission rate in the TDF-treated infants was significantly lower than the 92 percent rate in untreated animals ($P = 0.03$). In other studies of macaques treated with TDF for up to three years, van Rompay saw no evidence of bone toxicity.

Still, one may wish for something better than a 50-50 shot of winding up with HIV from breast milk, and this is where the grandmothers come in. Chandice Covington (University of California, Los Angeles) and Kenyan colleagues reasoned that many relatively young African grandmothers without HIV infection could resume lactation with a little mechanical help [abstract LbOOrB11]. If they produced enough high-quality milk to feed their HIV-infected daughters’ infants, they could cut the risk of breast milk transmission to zero.

Comparing milk from 22 grandmothers and their 22 infected daughters, Covington found equivalent secretory IgA, leukocytes, fatty acids, and other nutritious ladings. Six community focus groups confirmed strong support for grandmaternal breast feeding. Covington proposed that grandmothers’ milk may offer “an evolutionary loophole” that allows risk-free feeding.

Readers may not believe this at first, but those grandmothers bring us back to elephants.

**Elephants**

The AIDS elephant—the one who lent such pomp and gravitas to the opening ceremony and found himself accused of murder a day later—didn’t do it. Top-notch forensic work by the Royal Thai Police (no human remains on toes or tusks) exonerated the AIDS elephant from any involvement in the construction worker’s death. Apparently, the true assailant was an elephant who closely resembled him.

Elephants—beloved by Thais and by anyone who ever saw a circus parade—impress us with their uncomplaining constancy, their unassuming acuity, their idiosyncratic grace. But more than anything elephants impress with their sheer mass, their very conspicuity. What could be more obvious than an elephant? Perhaps the lactating potential of several million still-spry grandmothers untouched by HIV. Perhaps a feral epidemic that came down from the treetops and shows no sign of climbing back up.

But like the proverbial elephant in the living room, AIDS has proved remarkably easy to ignore. HIV infected another 4.8 million people last year and killed 2.9 million, both record highs. Yet global concerns have wandered elsewhere—to what? Terrorism? The threat of terrorism? Oil prices? To understand how a virus that has already killed more than the Black Death can become a matter of cavalier unconcern, one might cite its humdrum frequency. As perspicacious as any latter-day analyst, George Eliot construed this tendency in *Middlemarch* more than a century ago:

> We do not expect people to be deeply moved by what is not unusual. That element of tragedy which lies in the very fact of frequency, has not yet wrought itself into the coarse emotion of mankind; and perhaps our frames could hardly bear much of it.\(^{50}\)

But thousands of nameless bureaucrats, health workers, and volunteers do bear much of this epidemic’s brunt, committing their lives to slowing HIV. Meanwhile many of those who matter most—the leaders of AIDS-beleaguered nations—have chosen not to lead this fight.

A Thai spokesman decorously explained that the no-shows “were not comfortable with traveling here at this time.” Or perhaps the heads of Botswana, Brazil, Nigeria, Uganda, Rwanda, Canada, China, India, Russia, and the European Commission had more pressing matters than the 56 million HIV-infected adults\(^{49}\) lowering the life expectancy and devastating the economies of their countries (as they prepare to die).

Of course there is plenty of blame to go around, and most of us share in it. The world’s failure to come anywhere close to meeting the goals of the Global Fund to Fight AIDS, TB, and Malaria leaves an ugly blemish on global good will. The imminence of the WHO’s “3 x 5” plan to treat three million more people with HIV by 2005 beggars belief. And even a fully funded “3 x 5” would probably fall short by more than half, according to a study by Robert Hogg (University of British Columbia, Vancouver) [abstract ThPeB7243].

Hogg’s estimate rests on antiretroviral sales in 41 countries and demographic, economic, and epidemiologic data from those countries and 129 others. He used the UNAIDS 2001 “low estimates” of HIV prevalence to gauge the number of people with HIV. Taking the percentage of infected people who use antiretrovirals in Canada, the United States, and Western Europe as benchmarks, he estimated that 7.2 million people worldwide now need drugs for HIV.

George Eliot concludes her insight on the threat of too-acute perception thus:

> If we had a keen vision and feeling of all ordinary human life, it would be like hearing the grass grow and the squirrel’s heart beat, and we should die of that roar which lies on the other side of silence. As it is, the quickest of us walk about well waddled with stupidity.\(^{50}\)

Mark Mascolini writes about HIV infection, often as IAPAC Monthly’s writer at large (mailmark@ptd.net).
AIDS

Risk factors for hepatic decompensation in patients with HIV/HCV coinfection and liver cirrhosis during interferon-based therapy


OBJECTIVE: Hepatic decompensation was reported from two recent trials (APRICOT and RIBAVIC) assessing interferon (IFN)-based treatment of hepatitis C virus (HCV) in HIV/HCV-coinfected patients. This paper identifies risk factors associated with hepatic decompensation in APRICOT. METHODS: APRICOT is a randomized, partially-blinded, controlled trial comparing treatment with PEG-IFN alfa-2a 180 μg once weekly plus ribavirin/placebo 400 mg twice daily with IFN alfa-2a 3 million units three times weekly plus ribavirin 400 mg twice daily for 48 weeks in a total of 859 patients. Multiple logistic regression analysis was performed comparing the baseline characteristics of those cirrhotic patients who experienced decompensation with those of the other cirrhotic patients enrolled. RESULTS: Fourteen patients, all cirrhotic, experienced hepatic decompensation during the study. The incidence in the cirrhotic subgroup of the study was 10.4 percent (14/134). Six of the 14 patients died as a result of hepatic decompensation. The risk factors associated with hepatic decompensation were increased bilirubin, decreased hemoglobin, increased alkaline phosphatase or decreased platelets, and treatment with didanosine. Markers of viral replication, histological activity, cellular immune status or HCV therapy, treatment with ribavirin and pegylated versus non-pegylated IFN were not associated with hepatic decompensation. CONCLUSIONS: The results from APRICOT indicate that the overall risk of hepatic decompensation in HIV/HCV-coinfected patients without cirrhosis receiving IFN-based treatment is low. In contrast, patients with markers of advanced cirrhosis, despite the absence of a history of hepatic decompensation, should be monitored closely during IFN-based therapy, because they are at risk of hepatic decompensation. Treatment with antiretrovirals such as didanosine may increase the risk further.


Neurology

Higher frequency of dementia in older HIV-1 individuals: The Hawaii aging with HIV-1 cohort


BACKGROUND: Antiretroviral therapy has improved survival for HIV-1-infected individuals. The neuroepidemiologic implications of HIV-1 in an aging population are not well known, particularly the prevalence of HIV-associated dementia (HAD).

METHODS: The authors report a baseline cross-sectional analysis of 202 HIV-1-seropositive individuals enrolled into one of two groups of the Hawaii Aging with HIV Cohort: older (50 or more years old, n = 106) and younger (20 to 39 years old, n = 96). Neuropsychological, neurologic, medical, and laboratory data were obtained at enrollment. Participant cognitive status was classified (research case definitions) using American Academy of Neurology (1991) criteria in a consensus conference of physicians and neuropsychologists. RESULTS: HAD was more frequent in older (25.2 percent) compared to younger (13.7 percent) individuals (p = 0.041) corresponding to an OR of 2.13 (95 percent CI: 1.02 to 4.44) for the older compared to the younger group. After adjusting for education, race, substance dependence, antiretroviral medication status, viral load, CD4 lymphocyte count, and Beck Depression Inventory score, the odds of having HAD among individuals in the older group was 3.26 (1.32 to 8.07) times that of the younger group. CONCLUSIONS: Older age is associated with increased HAD in this HIV-1 cohort. Underlying mechanisms are unclear but do not appear related to duration of HIV-1 infection.


Sexually Transmitted Diseases

Estimates of the annual number and cost of new HIV infections among women attributable to trichomoniasis in the United States

Chesson HW, Blandford JM, Pinkerton SD.

BACKGROUND: Clinical evidence suggests that trichomoniasis facilitates the sexual transmission and acquisition of HIV. GOAL: The goal of this study was to estimate the annual number and cost of new HIV infections among women in the United States attributable to trichomoniasis. STUDY: We used a mathematical model of HIV transmission to estimate the probability that a woman with trichomoniasis-mediated increased susceptibility to HIV infection or as a result of increased HIV infectiousness in a trichomoniasis-infected male partner. RESULTS: Our results indicate that each year in the United States, an estimated 746 new HIV cases among women can be attributed to the facilitative effects of trichomoniasis on HIV transmission. The lifetime cost of treating these trichomoniasis-attributable HIV infections is approximately US$167 million.

CONCLUSIONS: Efforts to prevent trichomoniasis could help prevent HIV transmission and could reduce the economic burden associated with trichomoniasis-attributable HIV cases that occur each year. Because trichomoniasis is so common, however, a substantial number of cases would need to be detected and treated to have a discernible impact on HIV. Future research is needed to examine the cost-effectiveness of trichomoniasis prevention as a tool for HIV prevention.

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Oral Medicine

Oropharyngeal candidiasis in HIV-infected patients under treatment with protease inhibitors

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OBJECTIVE: Oropharyngeal candidiasis decreased when protease inhibitors were included with other antiretrovirals to treat HIV infection. We tested oral yeast isolates of Brazilian HIV-infected individuals receiving antiretroviral therapy for protease secretion and susceptibility to ritonavir and some antifungals. STUDY DESIGN: We collected oral samples and identified yeasts from 19 HIV-infected patients receiving highly active antiretroviral therapy (HAART) and suspected of having oral candidiasis. Ritonavir and its excipients’ effects on the isolated yeasts were tested for protease secretion by Rüchel’s technique. The yeasts’ susceptibility to amphotericin B (AnB), fluconosine (SFC), fluconazole (FZL), ketoconazole (KZL), and itraconazole (IZL) was determined by E-test (AB Biodisk). A chi-square test determined the statistical differences. RESULTS: Twenty-five different positive isolates were obtained. Sixty-eight percent were C. albicans. Other isolates included C. famata (16 percent), C. glabrata (4 percent), C. tropicalis (4 percent), T. capitatum (4 percent), and 1 isolate not identified. High protease secretion was observed for most of the isolates (20/25). Ritonavir only altered enzyme secretion in 6/20 of the protease-secreting isolates. All isolates were highly sensitive to both AnB and SFC. Antifungal activity did not change when ritonavir was added to the culture media. Some isolates were highly resistant to studied antifungals (52.2 percent KZL, 30.4 percent FZL, and 26 percent IZL). Resistance significantly decreased when ritonavir was added to the medium with KZL and IZL (P < 0.5 by chi-square). A trend to decreased resistance was also observed with FZL but the results were not statistically significant. CONCLUSION: Candida continues to be the most prevalent fungus in the oral cavity. Although oral candidal isolates secrete protease, ritonavir does not inhibit all protease-secreting oral yeast isolates. There seems to be a synergistic effect between ritonavir and oral antifungals against fungal resistance.

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The Evolution of ARV Therapy: Applying Clinical Trial Data to Optimize HAART in HIV Management

Learning Objectives:
- Relate recent clinical trial data concerning antiretroviral combinations that demonstrate suboptimal virologic outcomes
- List standard preferred and alternative regimens for antiretroviral-naive adults and adolescents with HIV according to nationally recognized guidelines
- State recommendations for the timing of initial antiretroviral therapy for the treatment of adults and adolescents with HIV according to nationally recognized guidelines

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Intended Audience:
This activity is intended for infectious disease and internal medicine physicians, and all those who treat HIV/AIDS.

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Focus on Hepatitis

Final APRICOT, ACTG A5071 results

Liz Highleyman

The final results from APRICOT and ACTG A5071—two major studies of hepatitis C (HCV) treatment in patients coinfected with HIV—published in a recent issue of the New England Journal of Medicine have prompted a prominent hepatologist to posit that a sustained virologic response can be achieved with pegylated interferon-alfa (PegIFN) and ribavirin (RBV) therapy in a substantial proportion of HIV/HCV-coinfected patients.

APRICOT

Francesca Torriani and colleagues presented data from Roche Laboratories’ APRICOT (or AIDS Pegasys Ribavirin International Coinfection Trial). The largest study of its kind, APRICOT included 860 HIV/HCV-coinfected participants in 19 countries who were HCV treatment-naive.

Participants were randomly assigned to one of three arms: 3 million IU standard interferon-alfa-2a three times weekly plus 800 mcg RBV daily (285 patients); 180 mcg pegylated interferon-alfa-2a (Pegasys, manufactured by Roche) once weekly plus placebo (286 patients); or the same doses of PegIFN plus RBV (289 patients), all for 48 weeks.

Baseline characteristics were similar in the three arms. About 81 percent were male, about 79 percent were white, about 10 percent were black, and the mean age was about 40 years. About 60 percent had genotype 1 HCV, 5 percent had genotype 2, 27 percent had genotype 3, and 7 percent had genotype 4. Participants had detectable baseline HCV RNA and elevated serum ALT. The mean total histological activity index (HAI) score was about 8.0, and about 16 percent had bridging fibrosis or cirrhosis. Subjects had stable HIV disease, with a mean CD4 count of about 530 cells/mm³; about 85 percent were on antiretroviral therapy and 60 percent had an HIV viral load below 50 copies/ml.

In an intent-to-treat analysis, 40 percent of patients treated with PegIFN/RBV achieved sustained virological responses (SVR), defined as undetectable HCV RNA at the end of a 24-week post-treatment follow-up period, compared with 20 percent of those receiving PegIFN monotherapy, and 12 percent of those receiving standard interferon/RBV (p < 0.001). Among patients with genotype 2 or 3, the corresponding SVR rates were 62 percent, 36 percent, and 20 percent, while in genotype 1 patients SVR was seen in 29 percent, 14 percent, and 7 percent, respectively. (For patients with HCV alone, SVR rates using PegIFN/RBV are about 80 percent for genotype 2 or 3, and about 45 percent for genotype 1).

Among patients with genotype 1, those with a baseline HCV RNA level greater than 800,000 IU/ml were significantly less likely to respond to any regimen than those with lower HCV viral loads (p < 0.001), but this difference was not seen in genotype 2 or 3 patients. Only two patients who failed to achieve an early virological response (at least a 2 log₁₀ reduction in HCV RNA by week 12) went on to achieve SVR (a negative predictive value of between 98 percent and 100 percent).

HCV therapy had no detrimental impact on HIV disease progression; in fact, HIV viral load decreased by about 0.7 log₁₀ copies in patients treated with PegIFN. Absolute CD4 counts decreased in all three arms (interferon reduces white blood cell levels overall), but CD4 percentages remained stable. HCV treatment success rates did not vary by baseline CD4 count or use of antiretroviral therapy.

In terms of safety and tolerability, 39 percent of subjects in the standard interferon/RBV arm, 31 percent in the PegIFN monotherapy group, and 25 percent in the PegIFN/RBV arm discontinued treatment for any reason (p < 0.001). The rates of serious adverse events judged to be treatment-related were 5 percent, 10 percent, and 8 percent, respectively. Neutropenia and thrombocytopenia were more common in the arms that included pegylated interferon. The rate of mitochondrial toxicity—a concern when RBV is combined with certain nucleoside reverse transcriptase inhibitors (NRTIs)—was low in all arms.

“[Our] results demonstrate that the current regimen used for the treatment of chronic hepatitis C alone can also be applied to patients coinfected with HIV and HCV,” the researchers concluded. “Peginterferon alfa-2a plus ribavirin has a favorable risk-to-benefit ratio when used to treat such patients, a substantial proportion of whom are likely to benefit from therapy with this combination.” They recommended that coinfected patients with genotypes 2 or 3 should be treated for 48 weeks, even though 24 weeks is sufficient for genotype 2 or 3 patients with HCV alone.

ACTG A5071

Raymond Chung (Massachusetts General Hospital, Boston) and colleagues published results from AIDS Clinical Trials Group (ACTG) A5071, the first randomized study comparing the safety and efficacy of standard interferon/RBV versus PegIFN/RBV in HIV/HCV-coinfected patients being treated for the first time.

A total of 133 participants were randomly assigned to receive either 6 million IU standard interferon-alfa-2a three times weekly for 12 weeks followed by 3 million IU three times weekly for 36 weeks (67 subjects), or 180μg pegylated interferon-alfa-2a (Pegasys) weekly for 48 weeks (66 subjects). Patients in both arms received daily ribavirin in escalating doses from 600 mg to 1,000 mg. Patients who did not achieve a virological response by week 24 underwent liver biopsy; those who showed histological improvement continued treatment.

Editor’s Note: Reprinted with permission from www.aidsmap.com (first e-published August 4, 2004).
Baseline characteristics were similar in both arms. About 82 percent were male, about half were white, about one third were black, and the mean age was about 44 years. About 78 percent had genotype 1 HCV. Subjects had detectable baseline HCV RNA and 67 percent had elevated serum ALT; the median fibrosis score was 2.0, the median HAI score was 5.0, and about 10 percent had cirrhosis. In this study, too, participants had well-controlled HIV; the median CD4 count was about 475 cells/mm³, about 60 percent had an HIV viral load below 50 copies/ml, and about 86 percent were receiving antiretroviral therapy.

After 48 weeks of treatment, 41 percent of patients in the PegIFN arm and 12 percent in the standard interferon arm showed an end-of-treatment response (p < 0.001). By 72 weeks, overall SVR rates were 27 percent in the PegIFN arm and 12 percent in the standard interferon arm (p = 0.03). Among subjects with genotype 2 or 3, SVR rates were 73 percent in the PegIFN arm and 33 percent in the standard interferon arm. For those with genotype 1, the corresponding rates were 14 percent and 6 percent.

Notably, while the end-of-treatment and SVR rates were the same in the standard interferon arm, the response rate declined dramatically during the follow-up period in the pegylated interferon arm; the relapse rate was especially high among patients with genotype 1. No patient who failed to achieve a 2-log reduction in HCV RNA by week 12 went on to achieve SVR (negative predictive value of 100 percent). Upon liver biopsy, about 35 percent of patients in both arms without virological clearance still showed evidence of histological response. Among patients with a virological response, 52 percent showed histological improvement.

As in the previous trial, HCV therapy had no adverse effect on HIV disease progression. Absolute CD4 counts decreased in both treatment groups, but CD4 percentages actually increased. Baseline CD4 count and use of antiretroviral therapy did not predict the likelihood of HCV treatment success, but having a detectable baseline HIV viral load was associated with SVR.

Both regimens were generally well tolerated; 12 percent in both arms prematurely discontinued therapy. This rate is similar to those seen in studies of patients with HCV alone using these regimens, but lower than those seen in previous studies of coinfected patients. One patient developed elevated lactic acid (a sign of mitochondrial toxicity), but did not require treatment discontinuation.

“In persons infected with HIV, the combination of [PegIFN] and [RBV] is superior to the combination of [IFN] and [RBV] in the treatment of chronic hepatitis C,” the authors concluded. “These regimens may provide clinical benefit even in the absence of virologic clearance.” They recommended that coinfected patients with advanced liver disease should continue IFN therapy even without a virological response “since the goal of treatment is slowing the progression of liver disease rather than eradicating the virus.”

Comparing APRICOTS and oranges?
It is unclear why the PegIFN/RBV SVR was so much higher in APRICOT (40 percent overall) than in ACTG A5071 (27 percent overall). In A5071, although a good end-of-treatment response rate was seen with this regimen, the relapse rate was high. This may be because the study started patients on a lower initial dosage of RBV relative to PegIFN/RBV; 12 percent in both arms prematurely discontinued treatment. This rate is similar to those seen in studies of patients with HCV alone using these regimens, but lower than those seen in previous studies of coinfected patients. One patient developed elevated lactic acid (a sign of mitochondrial toxicity), but did not require treatment discontinuation.

While the inconsistent results of these two studies are perplexing, and point to the need for further research, the impressive results seen in the APRICOT trial—the highest SVR rate yet seen in a coinfected population—provide reason for renewed hope.

In an editorial published in the same issue of the New England Journal of Medicine, Jean-Michel Pawlotsky (University of Paris XII, Créteil, France) discussed the treatment of hepatitis C in “difficult-to-treat” patients including those with HIV. The APRICOT and A5071 studies “show that a sustained virologic response can be achieved with pegylated interferon-alfa and [RBV] therapy in a substantial proportion of coinfected patients,” he wrote. Although SVR rates for coinfected patients remain lower than those for patients with HCV alone, ”[t]hese results, together with the poor prognosis for HIV-positive patients with HCV infection, justify broad use of antiviral therapy in the treatment of coinfected patients.”

References:
For more than two years 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 Sugata Mukhopadhyay, Surveillance Medical Officer with the National Polio Surveillance Project of the Government of India, based in Calcutta.

If you could live anywhere in the world, where would it be?  
Goa, located on the western Indian coast, has the most beautiful beaches in the world.

Who are your mentors or real life heroes?  
Netaji Subhash Chandra Bose, who dreamt of an undivided, secular India and sacrificed his life in the Indian freedom struggle.

With what historical figure do you most identify?  
Lord Krishna, whom people worship as a God; however he was one of the shrewdest politicians in the world who singlehandedly guided the “Pandavas” to the historical victory against the “Kanravas” in the great epic of “Mahabharata.”

Who are your favorite authors, painters, and/or composers?  

If you could have chosen to live during any time period in human history, which would it be?  
Ancient Egypt, with the pharaohs, pyramids, and sphinx. I do believe I was an Egyptian in my previous birth.

If you did not have the option of becoming a physician, what would you have likely become, given the opportunity?  
An actor and a philosopher.

In your opinion, what are the greatest achievements and failures of humanity?  
Achievements: Eradication of smallpox, invention of antibiotics and vaccines, and information technology. Failures: The human community is still divided by caste, creed, color, and religion.

What is your prediction as to the future of our planet one full decade from present day?  
1) India will be the worst hit country in the world by AIDS; 2) the eradication of poliomyelitis will be achieved, with progress made toward the eradication of the other diseases such as measles, hepatitis B, and rubella; 3) a nuclear war will destroy millions of lives in some sensitive part(s) of the world; and 4) we will discover extraterrestrial life.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?  
The world is the eternal battlefield against all odds and evils where every soul is sent with a mission, a duty to fulfill. So one has to live for a cause, not just for the sake of living.

What activities, avocations, or hobbies interest you?  
Creative writing, painting, collection of HIV/AIDS-related clippings from newspapers and magazines.
S A Y   A N Y T H I N G

Photo: Perry Smrz, IAPAC.
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