Can drugs catch up with HIV?

FEATURE: 12th Conference on Retroviruses and Opportunistic Infections
Can drugs catch up with HIV?

Mark Mascolini

The relentless evolution of HIV makes it a moving target for drug developers. Two new protease inhibitors—tipranavir and TMC114—may come closer to the bull’s-eye. But with few exceptions, progress with other antiretroviral classes seems slower.
José M. Zuniga

I resorted to using a cliché in summarizing for a newspaper reporter this month the messages conveyed in recent papers published in two respected medical journals; a communications faux pas most seasoned media pros are trained to avoid. Nonetheless, “the more things change, the more they stay the same” reverberated in my mind as I discussed the discovery of a rapidly progressing multidrug-resistant strain of HIV (MDR-HIV) found in a New York City patient, and the reality that for almost a decade a significant percentage of gay men in the United Kingdom diagnosed as HIV-positive received a late diagnosis.

To state the obvious, much has changed since the advent of antiretroviral therapy (ART), including an end to the immediacy of the death sentence an HIV diagnosis represented in the pre-ART era, and improvement of quality of life for those men, women, and children for whom access is not impeded by circumstance. Unfortunately, almost a decade into the ART era, some things have not changed enough to transform the way in which the AIDS epidemic is addressed in more affluent countries, given its tendency to evolve, sometimes in unpredictable ways, while at other times in the most predictable.

News of a “superbug” strain of HIV dominated the media last month, largely driven by a February 11, 2005, announcement by New York City Health Commissioner Thomas R. Frieden about a resident who had recently been infected with MDR-HIV and rapidly progressed to AIDS. The patient in question is in his mid-40s and admitted to regularly using crystal methamphetamine as well as engaging in unprotected receptive and insertive anal sex with multiple partners. Media-driven hysteria ensued as Departments of Health in other major US cities began to report the discovery of the “superbug” in their midst. Not even a late-breaker presentation delivered by David Ho and Martin Markowitz (Aaron Diamond AIDS Research Center, New York) at the 12th Conference on Retroviruses and Opportunistic Infections (CROI) last month in Boston quelled the furor. “Alarming,” some opined; “old news,” others argued.

Finally, Markowitz and colleagues published their data in the March 19, 2005, issue of The Lancet. The researchers’ findings are indeed alarming: “Our patient seems to have been recently infected by a viral variant of HIV-1 resistant to multiple classes of antiretroviral drugs. Furthermore, his virus population is dual tropic for cells that express CCR5 or CXCR4 coreceptor. The infection has resulted in progression to symptomatic AIDS in [four] to 20 months.”

Whether everyone will ever agree on the need for an announcement, or even on the science as reported in The Lancet, there are some truths that are unavoidable. Indeed, they must be spoken and addressed if we are to rein in what may be yet another onslaught by HIV. Those truths revolve around the intersection of HIV and recreational drugs, most notoriously crystal methamphetamine. And here is where the cliché applies, because as media reports and subsequent case study presentations were delivered and published, the long knives were unsheathed and bandied about in at times heated debate about the demonization of gay men by virtue of their behavior—debates not unlike those that took place more than 20 years ago in San Francisco around the closing of gay bathhouses as a means of stemming the AIDS epidemic in that epicenter.

There is a burgeoning epidemic of crystal methamphetamine use that threatens to undo years of progress made in both the prevention of new HIV infections and the treatment of both those who are already infected and those who may be by virtue of high-risk behavior. And, as important, there is a disquieting epidemic of risk-taking by HIV-negative and -positive people alike that is perpetuated by myriad psychological factors, not the least of which is a reclassification of HIV from “life-threatening” to “chronic.” How tragically ironic it would be to have advanced so much—reducing HIV-related morbidity and mortality through the widespread use of ART—only to find ourselves facing a new enemy that paralyzes our collective efforts.

Timothy Chadborn and colleagues (Health Protection Agency, Centre for Infections, London) published similarly disconcerting data in the March 25, 2005, issue of AIDS. In a day and age in which one would reasonably expect that voluntary counseling and testing (VCT)—the gold standard intervention widely advocated for ART scale-up in the developing world—should be the rule rather than the exception in the developed world, a review of national trends in England and Wales found otherwise. Late diagnosis—defined as a CD4 count <200 cells/mm³—was estimated in 31 percent of the 14,158 new diagnoses reported to the CD4 Surveillance Scheme from 1993 to 2002. This staggering number led researchers to conclude that, “The continued late diagnosis of one in four [men who have sex with men (MSM)] means these individuals lose the option to start therapy early, miss opportunities to prevent further transmission, and are
approximately 10 times more likely to die within a year of diagnosis.” The more things change…

It is easy to rest on our laurels in the post-ART era and, as we turn our individual and collective focus to Africa and other AIDS-ravaged regions of the world, ignore and thus allow to regroup an enemy that is wily beyond our every expectation. The public health implications—if not the humanitarian implications—of AIDS epidemics slipping out of control in the developed world are not an impossibility, but indeed a probability if our efforts are not redoubled in our respective backyards. ■

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IAPAC-AFRO, Southern African HIV Clinicians Society sign MOU for broad-reaching partnership in Africa

The leadership of the International Association of Physicians in AIDS Care (IAPAC) African Regional Office (AFRO) and Southern African HIV Clinicians Society (SAHIVS) signed a Memorandum of Understanding (MOU) last month through which the professional medical institutions will collaboratively advance initiatives on the African continent via a joint membership of 8,600 clinicians throughout Africa.

José M. Zuniga, IAPAC’s President/CEO (and Interim Executive Director of IAPAC-AFRO in Johannesburg), and SAHIVS President Des Martin predicted the broad-reaching partnership between the Africa-based institutions will significantly enhance and support efforts to scale up the delivery of antiretroviral therapy (ART) in Africa by strengthening health professional capacity around the delivery of HIV/AIDS care.

“IAPAC-AFRO considers our collaboration with a valuable strategic partner such as the SAHIVS as critical to our ongoing efforts to ensure that quality care, and specifically ART, is made available to millions of men, women, and children living with HIV/AIDS—care that is delivered by appropriately trained and adequately supported health professionals,” Zuniga said.

According to Martin, “Our strategic alliance with IAPAC-AFRO reinforces both institutions and allows us to add value to a membership of African clinicians and allied health professionals tasked with the monumental effort of delivering HIV/AIDS care, and especially ART, in resource-constrained settings.”

The July 2000 opening of IAPAC’s first regional office in Johannesburg marked the beginning of a notable chapter in the association’s history. The site for IAPAC’s first regional office was chosen after careful deliberation about how the association could best serve its most urgent challenge: Serving as a leader in responding to the global HIV pandemic, while ensuring that it achieved a relevant and effective role in the most severely HIV-affected regions of the world.

IAPAC is addressing this challenge by rapidly implementing concerted and sustained responses that will lead to measurable impact. IAPAC-AFRO’s objectives are to rapidly build infrastructure, develop capacity, and implement targeted programs that will produce beneficial and quantifiable outcomes. The regional office’s fundamental mission is to enable HIV-treating physicians to provide appropriate care for local HIV-infected populations and to mobilize a physician-activist membership that will advocate on behalf of its patients.

Zuniga said that a statement regarding IAPAC-AFRO’s new Executive Director will be forthcoming in April 2005. In the meantime, he announced the appointment of Jaz Hughes to serve as IAPAC-AFRO’s Deputy Director, effective March 1, 2005. ■
1. The introduction of protease inhibitors (PIs). David Ho (Aaron Diamond AIDS Research Center, New York) named *Time’s Man of the Year*, and PIs named *Science* magazine’s “breakthrough of the year.”

2. The demonstration of decreased rates of HIV transmission in Thailand.

3. The introduction of viral burden testing.

4. The demonstration that physician experience translates into a significant survival benefit.

5. The demonstration that use of azidothymidine (AZT) prophylaxis in HIV-infected women translates into dramatic reduction in vertical transmission.

6. The demonstration that *Mycobacterium avium* complex (MAC) prophylaxis with clarithromycin translates into a survival benefit.

7. The publication of guidelines to prevent occupationally acquired HIV in healthcare workers.

8. The introduction of nevirapine (NVP) as the first US Food and Drug Administration (FDA)-approved nonnucleoside reverse transcriptase inhibitor (NNRTI).

9. The establishment of highly active antiretroviral therapy (HAART) as the preferred method to treat HIV.

10. The demonstration of a survival benefit with saquinavir (SQV) plus ritonavir (RTV), the first combination of PIs that pharmacokinetically exploits RTV as a boosting agent.

References
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already a decade has passed since Louis Mansky and
Howard Temin discovered that HIV-1 cranks out one
mutation per genome per replication cycle. And antiretro-
virals haven’t caught up with the virus yet.

But it has not been for lack of effort.

Since early studies of nelfinavir (NFV) and bootless moil
to prove adefovir’s antiretroviral prowess, researchers
have struggled to devise drugs that rein in resistant virus.
Small battles have been won, but the big victories belong
to HIV.

That tide may have turned (until the next new moon,
anyway) at the 12th Conference on Retroviruses and
Opportunistic Infections (CROI) held this year in Boston.
The slide sessions on antiretroviral therapy (ART) show-
cased results on two protease inhibitors (PIs)—TMC114
and tipranavir (TPV)—that surpassed other PI options in
slowing resistant virus. Both studies involved people
with triple-class failure and plenty of protease mutations.

From the poster halls came word that triple-class fail-
ure itself may be on the wane, along with data confirming
improved long-term responses to potent up-front regi-
mens. But several groups agreed that year-in-year-out
viral suppression does not repay the CD4 debt amassed
by a prodigal HIV. And one team mapped a mortality
plateau after the post-1995 freefall.

Part I of the IAPAC Monthly’s 12th CROI review con-
strues those trends, along with some good news—and
some worrying news—on hepatitis coinfection. The May
2005 issue will report other clinically useful resistance
data, news on antiretroviral side effects, and dark develop-
ments in the epidemic among gay men.

**SALVAGE STARS**

The international phase 3 trials pitting TPV against other PIs
bear the memorable monikers RESIST 1 and 2. Researchers
scouting out the best dose of another resistance-routing
PI, TMC114, answered with POWER 1 and 2. The trial-
ming contest may be a dead heat. But because TPV’s
RESIST results made their first splash in late 2004,
TMC114 caused the bigger ripples at CROI.

Tipranavir and TMC114 were not the only ritonavir
(RTV)-boosted PIs scrutinized at the Boston conference.
Nor were PIs the only new resistance-ready antiretrovirals
surveyed. The conference also told two more knells in
obsequies for a once-favored resistance strategy—presal-
vage treatment interruption.

**TMC114 clears first hurdle handily**

Not until CROI’s penultimate slide talk did attendees
hear about what may be this year’s ultimate PI answer to
PI-resistant virus, Tibotec’s RTV-boosted TMC114.
People taking the highest dose of this resistance-con-
founding compound (600/100 mg twice daily) lopped
1.85 logs off their starting viral load in 24 weeks, while
people taking a comparison single or double RTV-boosted
PI whittled away only 0.27 log ($p < 0.0001$) [abstract
164LB]. Richard Haubrich (University of California, San
Diego) reported that nearly half of those taking 600/100 mg
of TMC114/RTV ended 24 weeks with a viral load under
50 copies/mL, compared with 9 percent in the control group.

With colleagues at 90 sites in 14 countries, Haubrich
randomized people with triple-class experience to one or
two licensed boosted PIs or one of four TMC114/RTV
doses—400/100 or 800/100 mg once daily, or 400/100
or 600/100 mg twice daily. The study group had a median
of three primary protease mutations (everyone had at least
one), and all enrollees started another set of antiretrovirals
picked to subdue their mutant horde.

The 497 trial participants began salvage with a mean
79-fold resistance to lopinavir (LPV), 38-fold resistance
to atazanavir (ATV), 29-fold resistance to saquinavir
(SQV), but only 4-fold resistance to TMC114. Equivalent
proportions in the TMC114 arms and the control arms
(about 15 percent) had tried the fusion inhibitor enfuvirtide
(ENF), and 8 percent once sampled TPV.

This heavily pretreated cohort had challenged HIV with
an average of 11 antiretrovirals. They had fairly advanced
disease, with a median CD4 count of 136 cells/mm$^3$ in
the TMC114 group and 163 cells/mm$^3$ in the control
arm. Baseline viral load averaged 4.61 logs in the
TMC114 group and 4.47 logs in controls (about 40,700 and
29,500 copies/mL). (See note 2 for more baseline details.)
The protocol blinded researchers to the TMC114 dose.
By week 24 the control arm had lost 51 people (51 percent), compared with 9 percent in the TMC114 groups. Toxicity rates looked similar in the TMC114 and comparison arms. While 4 percent stopped TMC114 because of side effects, 2 percent had treatment-limiting toxicity with comparison PIs. Notably, rash did not emerge as a TMC114 complication in this study, as it had in trials of unboosted TMC114.

The POWER team defined virologic failure as less than a half-log dip in viral load after week 8, less than a one-log drop after week 12, or consecutive loads a half-log above the lowest value reached. In a 24-week planned interim analysis using those criteria, Haubrich registered a 2 percent failure rate with TMC114 and a 43 percent rate with other PIs.

A noncompleter-equals-failure analysis found the steepest average 24-week viral load drop with 600/100 mg of TMC114/RTV twice daily:

- 600/100 mg twice daily (n=64): -1.85 logs (p<0.0001 versus control, p<0.05 versus 400/100 mg once daily)
- 400/100 mg twice daily (n=64): -1.74 logs (p<0.0001 versus control)
- 800/100 mg twice daily (n=61): -1.43 logs (p<0.0001 versus control)
- 400/100 mg once daily (n=66): -1.34 logs (p<0.0001 versus control)
- Control (n=74): -0.27 log

While 47 percent taking the 600/100-mg dose reached a 24-week load below 50 copies/mL in a noncompleter analysis, only 9 percent taking a comparison PI regimen reached that mark (p<0.01). With the same type of analysis to figure sub-50-copy rates, the highest dose of TMC114 outdid the control PIs in subgroups of ENF-naive people starting that entry blocker (67 percent versus 16 percent), people not taking ENF (37 percent versus 8 percent), and people having three or more primary PI mutations (48 percent versus 5 percent), having more than 4-fold baseline susceptibility to TMC114 (45 percent versus 5 percent), or starting no other antiretrovirals rated active at baseline (31 percent versus 0 percent).

Tighter viral control with 600/100 mg of TMC114/RTV translated into the best CD4 gain in that group (75 cells/mm³), compared with 50- to 55-cell jumps with the other TMC114 doses and a 15-cell uptick with the other combinations.

As good as these results look, it bears remembering that they represent 24 weeks of data from a trial subset. POWER 1 and 2 will continue through 96 weeks while researchers plan phase 2 studies to test the 600/100-mg twice-a-day dose.

**TPV sooner — or TMC114 later?**

Clinicians with candidates for TMC114 will probably have to make a tough choice by year’s end—whether to assail that PI-resistant virus with TPV/RTV or whether to wait for the TMC alternative. Reports at this year’s CROI detailed resistance-specific responses to TPV/RTV [abstract 104] and dovetailed the two RESIST trials to compare TPV/RTV with LPV/RTV [abstract 560].

RESIST enrollees shared some baseline traits with the POWER cohorts assembled to test TMC114: RESIST participants randomized to TPV/RTV started with a median viral load of 4.82 logs (around 66,000 copies/mL) compared with 4.61 logs (about 40,700 copies/mL) among people starting TMC114/RTV in POWER. Respective median baseline CD4 counts measured 155 cells/mm³ in RESIST and 136 cells/mm³ in POWER.

While 60 percent assigned to TPV/RTV in RESIST claimed three or four primary PI mutations, three was the median primary mutation number in POWER. Median numbers of antiretrovirals on study entry charts were 12 in RESIST and 11 in POWER. Everyone in both trials had triple-class experience, and everyone got a resistance-tuned background regimen plus their new PIs. Instead of defining virologic failure benchmarks, as in POWER, the RESIST team defined response as at least a 1-log (10-fold) drop in viral load.

RESIST researchers randomized 582 people to start 500/200 mg of TPV/RTV twice daily and 577 to start LPV/RTV, SQV/RTV, indinavir (IDV)/RTV, or amprenavir (APV)/RTV. Six months later, David Cooper (University of New South Wales, Sydney) figured a 39.6 percent response rate in the TPV/RTV group versus 21.4 percent with LPV/RTV (p<0.0001) by a noncompleter-equals-failure analysis [abstract 560]. Among LPV-naive people, though, the better 24-week response with TPV did not significantly exceed that with LPV (45.3 percent versus 36.1 percent).

A 24-week noncompleter comparison between TPV/RTV and the combined comparison arms showed a consistently better response to TPV/RTV according to the number of other background antiretrovirals rated active at baseline:

- Zero: TPV 13.1 percent versus control 9.1 percent
- One: TPV 37.4 percent versus control 12.9 percent
- Two: TPV 46.2 percent versus control 19.9 percent
- Three or more: TPV 54.7 percent versus control 34.3 percent
- Overall: TPV 41.2 percent versus control 18.9 percent
In a more detailed resistance analysis, Jonathan Schapiro (Sheba Medical Center, Tel Aviv, and Stanford University) considered three sets of baseline mutations—(1) all changes from the protease consensus sequence, (2) primary mutations at codons 30, 46, 48, 50, 82, 84, and 90, and (3) substitutions at codons 33, 82, 84, and 90, mutations originally rated particularly troublesome for TPV [abstract 104].

Tipranavir/RTV outperformed the other RTV-boosted PIs in comparisons based on all three mutation sets. Among people with one or more primary mutations (set 2), more people randomized to TPV/RTV lowered their viral load at least 1 log (10-fold) by week 24:

- One or two: TPV 40.9 percent versus control 28 percent ($p = 0.0067$)
- Three or four: TPV 42 percent versus control 14.6 percent ($p < 0.0001$)
- Five or six: TPV 44.4 percent versus control 16.7 percent (not significant)

Despite the nonsignificant difference in the third comparison, the 1-log response rate to TPV/RTV stayed steady as primary mutations piled up, while the response to comparison PIs dropped after two appeared. How tightly a PI keeps HIV in its clutches as mutations stack up is literally a matter of hanging on, explained François Clavel (Bichat-Claude Bernard Hospital, Paris) in a symposium lecture [abstract 180].

Protease inhibitors work by catching hold at the very center of the butterfly-shaped protease protein. A few protease mutations disrupt drug binding in this pocket, Clavel noted, but most do not. These other mutations pop up all over the protein’s “wings” and stretch the binding pocket ever wider, loosening the PI’s grasp. Think of climbing a tree, Clavel proposed. You do best when you use both hands and both feet. If you hang from the tree with only one hand—as a PI does when the binding pocket yawns—shaking the tree just a little makes you fall: When enough mutations emerge, just one more makes the virus resistant. Although Clavel did not extend his analogy of TPV, it seems to take more mutational “shaking” to knock TPV out of the protease tree.

Among people with 12 or fewer protease mutations, the median viral load dropped 1.85 logs with TPV/RTV (versus 0.44 log with control PIs, $p < 0.0001$). In this analysis TPV maintained a significant edge over the other boosted PIs as the baseline mutation number climbed: -0.63 versus -0.42 log for 13 to 15 mutations ($p = 0.0105$) and -1.08 versus -0.16 log for 16 to 18 mutations ($p < 0.0001$). When faced with 19 or more mutations, TPV/RTV finally ran out of steam but still nipped replication significantly better than comparison PIs, by -0.36 versus -0.2 ($p < 0.0001$).

The four mutations once judged prime TPV nemeses—at positions 33, 82, 84, and 90—did not slow this new PI more than others in Schapiro’s resistance shakedown. But a deeper analysis, he reported, turned up 21 mutations that may conspire to curtail responses.3

### Table 1. How TPV/RTV and TMC114/RTV did at 24 weeks*

<table>
<thead>
<tr>
<th></th>
<th>TPV/RTV 500/200 mg twice daily ($n = 582$)</th>
<th>TMC114/RTV 600/100 mg twice daily ($n = 64$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 copies/mL (%)</td>
<td>23.9</td>
<td>47</td>
</tr>
<tr>
<td>Median drop in viral load</td>
<td>-1.85†</td>
<td>-1.85†</td>
</tr>
</tbody>
</table>

*Not a cross-study comparison. All results from noncompleter-equals-failure analyses.
†The viral load change in the TPV group is the median for everyone with 12 or fewer protease mutations at baseline. The change in the TMC114 group includes everyone taking 600/100 mg twice daily. Median numbers of baseline protease mutations were 16 in the TPV study and 18 in the TMC114 study.

Sources: Jonathan Schapiro, abstract 104; Richard Haubrich, abstract 164LB.

A mutation score based on that arm-long list may emerge with further study. If it does, clinicians not already privy to expert resistance counsel will have to find a friendly expert fast.

Are there hints on how TPV and TMC114 compare in people with PI-resistant virus? Cross-study comparisons, all readers know, are statistically unsupportable, probatively problematic, and sometimes downright dangerous. But HIV clinicians and the people they treat live dangerously, and they’ll have to weigh some data or other if deciding whether to try TPV (maybe late this year) or to hold out for TMC114. As already noted, baseline traits looked similar in the RESIST and POWER studies, and work so far shows no toxic surprises with either PI. So, if you are bold, consider Table 1.

If trends in Denmark mirror wider tendencies, cobbling together combinations for people with triple-class failure may be a rarer exercise as time goes by. Nicolai Lohse (Odense University Hospital, Odense, Denmark) and colleagues across Denmark charted drops in triple-class failure among both ART-naive and -experienced people beginning around 2001 [abstract 594] (see “Better response rates,” page 79). No one will be sorry if the market for quirky rescue regimens peters a bit in coming years. It will surely stay big enough to encourage further antiretroviral development.

### ATV as a salvage drug

Atazanavir has earned favor as a page-one PI because of its once-daily dosing and steadfast disinterest in stirring lipids or glucose. But for people with a handful of PIs in their treatment history, can ATV help bring HIV to heel? One CROI study found synergy between ATV and SQV against ATV-resistant but SQV-susceptible virus. Other work uncovered one salvage combo that bears close watching—ATV plus nevirapine (NVP)—but not for good reasons.

The ATV/SQV study involved three site-directed mutants with two to four mutations and low-level resistance to ATV and/or SQV and 11 clinical isolates with four to nine mutations and higher levels of resistance to the PIs [abstract 715]. Sophie Lebel-Binay (VIRalliance, Paris) gauged inhibition of these viruses at four ATV/SQV ratios—1:1, 2:1, 4:1, and 8:1.
She found no hint of synergy against wild-type (nonmutant) virus but significant synergy at all four PI ratios for a virus in which the I50L and A71V mutations yielded low-level resistance to ATV (5.35-fold change in 50 percent inhibitory concentration [IC50]) and susceptibility to SQV (0.66 fold change in IC50). The PIs also proved synergistic against two other SQV-susceptible viruses.

What do these findings mean? Lebel-Binay noted that synergy rose with each higher ATV/SQV ratio—a finding strongly suggesting that ATV somehow enhances SQV activity. One possibility, she proposed, involves higher intracellular SQV levels, perhaps because of saturation of intracellular proteins or inhibition of drug transporters by ATV. The same thing happened in an earlier study of LPV/SQV that measured synergy against virus with high resistance to LPV and less to SQV. And other research clocked long intracellular SQV half-lives compared with other PIs.5

Together with work charting higher ATV and SQV exposure when RTV boosts the paired PIs rather than each PI singly,6,7 Lebel-Binay’s findings position ATV/SQV/RTV as a rescue regimen worth study—at least in people with resistance to ATV but not SQV.

On the other hand, ATV probably should not replace RTV as an SQV booster in people just starting PIs. That conclusion emerged from a study of eight healthy men and seven hardy women who volunteered to take SQV/ATV at doses of 1,600/400 mg and 2,000/400 mg once daily for 10 days [abstract 655]. Stephen Becker (Pacific Horizon Medical Group, San Francisco) charted significantly higher SQV exposure with an RTV boost at a once-daily dose of 1,600/100 mg. Notably, levels of all three PIs climbed higher in the women than in the men even after statistical adjustment for weight (p <0.05).

The potential dangers of ad hoc salvage concoctions came to light in a study of 100 people taking ATV [abstract 656]. Measuring ATV troughs in this group, Alan Winston (University of New South Wales, Sydney) recorded levels below 50 µg/L in some of them, all of whom had an undetectable viral load. Only one variable predicted low ATV levels in a multivariate analysis—cotherapy with nevirapine (NVP) (mean ATV trough 350 µg/L with NVP and 726 µg/L without, p=0.011). In the same analysis only RTV boosting independently predicted a higher ATV trough. Factors such as fat content of meals, drinking buffered beverages, and adherence did not affect ATV troughs.

Clinicians questioned study participants about other prescription, nonprescription, and herbal medicines they took with ATV. Although an earlier study found 76 percent lower ATV exposure among people taking 40 mg of omeprazole with 300/100 mg of ATV/RTV,8 ATV levels proved no lower in 12 people taking that stomach acid quencher in Winston’s cohort. Two factors may explain the lack of an omeprazole-ATV interaction, Winston suggested: 10 of the 12 people taking omeprazole took it at least 10 hours earlier or later than ATV, and two took only 20 mg daily.

Only further study can determine whether people need a higher ATV/RTV dose with NVP, Winston cautioned. But the findings offer an admonitory notice on possible risks of untested antiretroviral combinations.

One other notable CROI report on ATV—to be detailed in part 2 of this article—came from Eoin Coakley (ViroLogic), who documented what seems to be the first case of ATV/RTV failure with primary resistance to ATV mediated by the N88S mutation, a change not seen earlier in the clinic without ATV’s signature mutation, I50L [abstract 716].

Resistance to the sole entry inhibitor

Envelope (env) is HIV’s most volatile gene—not a surprise when one considers the de d gymnastics env evolved to escape neutralizing antibodies. What do these skittish gyrations mean for resistance to ENF, a drug often mixed into incompletely suppressive salvage regimens?

To find out, a team from François Clavel’s lab, headed by Beatrice Labrosse (Bichat-Claude Bernard Hospital, Paris), tracked env evolution in six people starting ENF as part of a salvage mélange and followed for 12 to 50 weeks [abstract 97]. She found highly variable baseline susceptibility to the fusion inhibitor. But regardless of that baseline value, the virus stubbornly hatched new resistance mutations in the heptad repeat (HR1) region of viral gp41 until high-level resistance emerged.

In every case these HR1 mutations arose from an env quasispecies different from the one dominant before ENF therapy. (A quasispecies consists of all viral variants that make up a population in one person.) In four of the six people the post-treatment env sequences proved more fit than those cataloged at baseline.

These findings appear to mean that envelope’s whole genetic repertoire plays “a critical role in the expression and selection of HR1 mutations,” Labrosse suggested. In other words, Clavel proposed in his review lecture [abstract 180], involvement of the whole env quasispecies could facilitate emergence of resistance to ENF and preserve replication capacity.

And virus resistant to ENF appears to pop up posthaste when an ENF regimen flounders. Sequencing virus from 30 people when they started ENF salvage and repeatedly over the next few weeks, George Beatty (University of California, San Francisco) spotted ENF resistance mutations immediately upon viral rebound, and viral loads typically rushed right back toward baseline [abstract 581]. Although no commercial assay tracks ENF mutations, clinicians should suspect failure of an ENF regimen when it does not trim the viral load, or when it does and the load rebounds.

A (minor) role for replication capacity?

Fervid research in the past few years has sought to divine the impact of resistance on viral replication capacity, and
the effect of replication capacity on disease progression. So far, though, this work has not driven clinicians to add replication capacity—or RC—to their prognostic tool kit. New work by Andrea De Luca (Catholic University, Rome) nominated high RC as a useful guide to rescue therapy [abstract 692]. But resistance remained a better predictor of long-term response.

With ViroLogic colleagues (who developed an RC assay), De Luca looked at viral susceptibility and RC in people from the ARGENTA trial, which tested the merits of genotyping to elect a new regimen after virologic failure. In the 139 people De Luca analyzed, a higher (better) baseline phenotypic susceptibility score correlated significantly with a sharper drop in viral load through 34 months of follow-up (p = 0.011) and with a bigger CD4 boost through 18 months (p = 0.039).

Replication capacity correlated positively with the number of baseline drugs to which HIV proved susceptible on phenotyping (R = 0.034, p < 0.001). For every PI tested, mean RC proved significantly higher in PI-susceptible virus than in PI-resistant virus (p < 0.01 for APV, ATV, IDV, LPV, NFN, RTV, and SQV). For each PI, a lower RC meant a significantly decreased susceptibility to that drug.

People with an RC above 65 percent gained significantly more CD4 cells through 24 months of follow-up than did people with a lower RC (approximately +40 versus -80 cells/mm3, p = 0.007). A higher RC also correlated with a worse three-month virologic response in people who did not control HIV and after stratification for the number of drugs to which HIV proved susceptible at baseline.

But in a univariate Cox regression model, RC did not predict a higher risk of clinical progression, whereas US Centers for Disease Control and Prevention (CDC) class C disease, older age, and CD4 and RNA changes did. The protease mutations K20M/R and I84V also ratcheted up the risk of progression in this analysis (K20M/R hazard ratio [HR] 5.41, p = 0.0003; I84V HR 2.74, p = 0.03).

Resistance, De Luca concluded, remains a stronger driver of RNA and CD4 response to rescue therapy. He proposed that susceptibility testing — phenotyping — should be “the primary tool” to guide treatment decisions after ART failure. But in people who cannot stop replication with salvage therapy, De Luca suggested, “replication capacity can be a secondary tool to drive the treatment decision.”

The novel and the not-so-new

The parade of antiretrovirals termed “novel” has not slowed since the first CROI. To the dismay of many but the surprise of none, most of these elixirs never get named on a prescription pad. Predicting eventual winners remains a chore that shames both drug development doyens and Wall Street panjandrums.

To stand a chance in today’s florabundant antiretroviral market, any new drug must do something special—stop virus via some unique modus operandi, strangle off resistant strains, or go down like honey. A viral maturation inhibitor from Panacos Pharma met the first criterion. Aside from the new PIs discussed above, a fresh nonnucleoside reverse transcriptase inhibitor (NNRTI) from Tibotec met the second. Alas, dogged research has yet to integrate an integrase inhibitor into antiretroviral plans, as attendees learned in hearing the first clinical trial results of such a drug.

PA-457, the Panacos aspirant, stymies maturation of the viral capsid protein p24 (yes, the protein once used to gauge antiviral response) and so renders new virions impotent [abstract 159]. A double-blind study tested single doses of PA-457 in 24 HIV-infected people who had not taken antiretrovirals for at least four weeks, reported Panacos researcher David Martin.

Twenty days of follow-up showed a significant dose-response relationship (p < 0.05) with median viral load dips of 0.17 log with placebo, 0.27 log with 75 mg of PA-457, 0.45 log with 150 mg, and 0.5 log with 250 mg. Viral suppression with the two highest doses, though not huge, matched results in single-dose studies of other antiretrovirals, Martin noted. And the solitary dose kept viral loads down for 10 days.

Two people started the study with multiresistant virus. One person assigned to 250 mg had the L210W, K103N, and Y181C reverse transcriptase mutations plus the V771 and L90M protease mutations. Nonetheless, that person’s viral load fell 0.73 log. Despite starting treatment with the M184V and K103N reverse transcriptase substitutions and L10I and V771 in protease, a person taking 150 mg of PA-457 notched a 0.53-log RNA drop. No notable side effects marred this single-dose study. PA-457 efficacy trials will start later this year.

Tibotec is putting money on two NNRTI ponies with activity against virus resistant to NVP and efavirenz (EFV). The first, TMC125, looked good in test tube studies aired at last year’s CROI. The second, TMC278, started its clinical run for the roses this year in a three-country sprint presented by Frank Goebel (Ludwig Maximilians University, Munich) [abstract 160]. With colleagues in Russia and Britain, he tested five doses—25, 50, 100, and 150 mg—given once daily for seven days to 44 people, and no resistant virus emerged. A multinational phase 2 study has begun.

Viral load drops averaged 1.77 logs with 400 mg of a Merck integrase inhibitor given as twice-daily monotherapy for 10 days to treatment-naive and -experienced people, and 1.73 logs with 200 mg [abstract 161]. Susan Little (University of California, San Diego) reported respective CD4 vaults of 89 and 73 cells/mm3 in those 10 days. Six of 16 people taking the higher dose reached a viral load...
below 400 copies/mL. But the development gauntlet for integrase inhibitors still has no end in sight: Merck had to shelve this compound when toxicities arose in animal studies. The company will now try a related agent.

Two other drugs with dog-eared development dossiers—the nonnucleoside capravirine and the nucleoside amdoxovir (DAPD)—did not fare terribly well in regimens tooled for people with treatment experience. The nonnucleoside trial teamed 700 or 1,400 mg of capravirine twice daily (or placebo) with NFV and hand-picked nucleosides in 179 people with NNRTI-resistant virus but no PI experience [abstract 555]. Baseline loads averaged 4.4 logs (about 25,000 copies/mL) and average starting CD4 counts were in the low 200s. Earlier work indicates that capravirine has some activity against NNRTI-resistant virus.

After 48 weeks viral loads dropped 2.1 logs in the placebo group, 2.3 logs in the 700-mg group, and 2.4 logs in the 1,400-mg group. Defining failure as less than a half-log RNA decline by week 4 or a half-log drop followed by a rebound, Pfizer’s Rick Pesano chalked up a 48-week failure rate of 24 percent with placebo, 15 percent with 700 mg of capravirine, and 13 percent with 1,400 mg—nonsignificant differences. Dropout rates were high: 44 percent with placebo, 42 percent with 700 mg, and 30 percent with 1,400 mg. The overall poor response seems odd since everyone started NFV without PI experience.

Because the nucleoside reverse transcriptase inhibitor (NRTI) amdoxovir thwarts virus resistant to zidovudine (AZT) and lamivudine (3TC), Barbara Gripshover (University Hospital of Cleveland) and US AIDS Clinical Trials Group (ACTG) mates added it or placebo to a salvage regimen including ENF and three to five other drugs for 18 people with medians of six NRTI mutations, one NNRTI mutation, and seven PI mutations [abstract 553]. This group began salvage with an abysmal CD4 count of 36 cells/mm3 (range 11 to 537 cells/mm3) and an average starting viral load of 100,000 copies/mL.

The runaway baseline resistance proved too tough even for a regimen boasting two drugs with novel resistance profiles. In 24 weeks the mean viral load slipped 1.11 logs among the nine people randomized to amdoxovir and 0.8 log in the placebo group, a nonsignificant disparity. Three of nine people taking amdoxovir versus one of nine taking placebo reached a viral load below 200 copies/mL. And the average CD4 count climbed 70 cells/mm3 with amdoxovir versus 54 cells/mm3 with placebo (also nonsignificant). Gripshover recorded six new AIDS diagnoses and two deaths, with no advantage for the amdoxovir arm.

But because the drug showed some activity in this advanced group, the ACTG urged further study. Whether that will happen remains unclear because Gilead dropped development of amdoxovir last year and turned the license back to Emory University and the University of Georgia Research Foundation.

**Two more dead-end STI salvage studies**

One day clinicians will stop studying structured treatment interruptions (STIs) as a way to prime virus for salvage therapy. The odds on success with that tactic got longer yet at CROI, as two more groups found no advantage with a presalvage break versus immediate therapy. For those still keeping score, that makes it five to one for the “no benefit” team.

People in Canada have apparently kept pace with STI salvage news, because a randomized trial of a 12-week STI versus immediate treatment had to close accrual early with a dearth of enrollees [abstract 580]. Still, Sharon Walmsley (University of Toronto) and coworkers randomized 67 people to each study arm. Study participants had to have at least two active antiretrovirals they could put in a new regimen. All started three to five drugs with plentiful treatment experience but with relatively well-controlled HIV infection (median viral load 3.9 logs in both groups; median CD4 count 320 cells/mm3 in the STI group and 360 cells/mm3 in the control group).

After 60 weeks of follow-up, Walmsley saw no virologic differences between the groups but a significant CD4 deficit in the STI arm. While 43 people (64 percent) in the control arm reached a sub-50-copy load at least once, 53 people (79 percent) in the immediate-treatment group reached that mark. The median viral load drop at week 60 measured 1.7 logs in both arms.

The STI covey lost an average 80 cells/mm3 during their drug break and never caught up with the control arm. After 60 weeks of follow-up median CD4 gains measured 25 cells/mm3 in the STI takers and 95 cells/mm3 in the immediately treated (p = 0.04). Although that difference may seem clinically marginal to groups starting the trial with more than 300 cells/mm3, the early ebb in the STI arm caused trouble for at least one and maybe four people. Despite a protocol stipulation to start Pneumocystis prophylaxis if the CD4 count fell under 200 cells/mm3, one person ended up with Pneumocystis pneumonia at week 7. Two others endured Candida esophagitis (at weeks 28 and 43), and one had lymphoma by week 57. No one in the immediate-treatment group added an AIDS diagnosis during the study.

The already mentioned study by George Beatty (University of California, San Francisco) enrolled 30 people with much more advanced HIV infection (median baseline CD4 count 39 cells/mm3, range 12 to 135 cells/mm3) and with resistance to at least two NRTIs, at least one NNRTI, and at least two PIs [abstract 581]. With Steven Deeks (University of California, San Francisco), Beatty cited earlier work in hypothesizing that treatment breaks may work for people with multidrug-resistant virus who can build a new combo around a drug from a novel class, such as ENF. But that didn’t happen in this study of 15 people who took a 16-week STI before starting an ENF regimen and 15 who started salvage pronto.
Twenty-four weeks after randomization (six weeks after treatment began in the STI arm), both groups saw about 1.5 logs off their viral load, and that lack of difference persisted through week 48. At 24 weeks eight of 15 people (53 percent) in the immediate arm and five of 14 (36 percent) in the STI group had a viral load under 75 copies/mL, a nonsignificant difference. CD4 counts rose about 100 cells/mm³, on average, through week 48. During the drug break median CD4s swooned 27 cells/mm³ from an already treacherous baseline of 47 cells/mm³.

Baseline susceptibility to ENF did not predict virologic outcome, but overall susceptibility to the salvage regimen did. Everyone with a phenotypic susceptibility score at or below 1 had a virologic failure during salvage, whereas 63 percent with a score above 1 had an undetectable load at 24 weeks.

Final results of the already published CPCRA 064 study confirmed a persistent CD4-cell tumble after 24 weeks of treatment in the STI arm (-3.2 cells/mm³ versus +39.6 cells/mm³) in the immediate-treatment group, \( p = 0.07 \) [abstract 579]. Jodi Lawrence (University of California, San Francisco) reported 44 cases of disease progression in the group that took a four-month drug holiday before salvage versus 29 in the control group (1.66 hazard ratio adjusted for baseline CD4, viral load, AIDS diagnoses, and study site, \( p = 0.04 \)).

### Values of avoiding drug breaks

Compared with proving the merits of stopping therapy for people with resistant virus and risky CD4 ratios (see preceding section), proving the virtues of continuing therapy for such people seems almost simple. Daniel Kaufmann did it in the Swiss HIV Cohort Study, Veronica Miller did it in the Frankfurt and EuroSIDA cohorts, and now Isabelle Kousignian (Pierre and Marie Curie University, Paris) has done it in the French Hospital Database on HIV [abstract 592]. Even with the lowest CD4 counts and detectable viral loads, she reported, maintaining ART wards off AIDS diagnoses.

Kousignian and colleagues charted new AIDS-defining diseases in five groups:

1. No ART (\( n = 3,050 \))
2. Monotherapy only (\( n = 10,560 \))
3. Combination antiretrovirals with a treatment interruption of at least three months (\( n = 1,047 \))
4. Combination antiretrovirals without interruption and two or more viral loads above 500 copies/mL (\( n = 4,563 \))
5. Combination antiretrovirals without interruption and two viral loads below 500 copies/mL (\( n = 3,008 \))

The median treatment hiatus measured 4.6 months (interquartile [IQR] range 2.7 to 8.9 months).

As one might expect, the overall rate of new AIDS diagnoses proved significantly higher in the untreated and monotherapy groups than in the other three groups. And new AIDS rates proved lowest among people who kept their viral load under 500 copies/mL (group 5). The most interesting comparison involves groups 3 and 4. Group 4 (people with virologic failure but no break from potent therapy) did significantly better in averting AIDS than group 3 (people who interrupted potent therapy) regardless of CD4 count (Table 2).

The adjusted hazards ratio for a new AIDS diagnosis in the no-break group 4 measured 0.60 (95 percent confidence interval [CI] 0.51 to 0.72) compared with the treatment interruption group 3 (\( p = 0.0001 \)). In other words, sticking with therapy instead of taking a holiday lowered the risk of a new AIDS complication by 40 percent even when treatment lost control of viral replication.

Other interesting disease-specific findings emerged: The treatment break cohort had a higher rate of fungal infections than all other groups—even the untreated and monotherapy contingents. And compared with the untreated or monotherapy groups, the treatment interrupters had the same rates of *Pneumocystis* pneumonia, toxoplasmosis, and pulmonary or esophageal candidiasis. For people in the French Hospital Database, holidays from potent therapy meant sailing back to the monotherapy era.

### Table 2. New AIDS diagnosis rate* with or without breaks from potent therapy

<table>
<thead>
<tr>
<th>CD4 stratum</th>
<th>Treatment break (n = 1,047)</th>
<th>No break but RNA &gt;500 copies/mL (n = 4,563)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 50 cells/mm³</td>
<td>58.0 ± 11.0</td>
<td>44.4 ± 4.6</td>
<td>0.0009</td>
</tr>
<tr>
<td>50 to 200 cells/mm³</td>
<td>10.6 ± 2.9</td>
<td>7.0 ± 0.9</td>
<td>0.0035</td>
</tr>
<tr>
<td>Any CD4 count</td>
<td>20.5 ± 3.7</td>
<td>14.3 ± 1.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Events per 100 person-years.

Source: Isabelle Kousignian, abstract 592.

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### TREATMENT TRENDS 2005

Antiretroviral history is replete with stirring advances, rueful setbacks, and the odd thunderclap. But more than anything that history is replete with repeats, building a record of almost soporific sameness as the best regimens and soundest strategies rise like fine cream in study after study.

The just-reviewed virtues of continuing—rather than suspending—therapy for people with advanced disease and scant options have resounded for a half decade. The same span has elapsed since first reports from Dupont’s 006 study installed EFV and two NRTIs in the firmament of simple, durable first-line regimens. The 12th CROI showed, again and again and again, that this frill-free trio is hard to beat.

### Something not new: EFV + two NRTIs

Mounting long-term, massive, multinational trials—difficult by definition—can have its rewards when the \( p \) power...
grows big enough to show that one regimen, or one strategy, clearly outperforms rivals. But these megatrials can also have a hollow ring when their length leaves an anachronistic echo.

INITIO, begun in the last century, now seems a victim of remorseless time. As in ACTG 384, unveiled 2.5 years ago at the XIV International AIDS Conference in Barcelona, Australian and French INITIO collaborators found that EFV with two nucleosides works better than NFV plus two nucleosides as first-line therapy [abstract 165LB]. And as in the ACTG trial, a four-drug regimen piggybacking EFV and NFV with two NRTIs lagged the simpler EFV combo.

All of INITIO’s initial regimens rested on didanosine/stavudine (ddI/ddT), reported Patrick Yenin (Bichat Hospital, Paris). As a result, lots of people switched to new nucleosides over the median 3.7 years of follow-up. But significantly fewer people had to stop or switch from EFV/ddI/ddT (44 percent) than from those NRTIs plus NFV (63 percent) or EFV/NVF (76 percent) over the study’s course. An intent-to-treat analysis after three years showed significantly more sub-50-copy responses in the EFV/ddI/ddT arm:

- EFV/ddI/ddT: 74 percent <50 copies/mL (p = 0.004 versus NFV arm, p = 0.003 versus EFV/NVF arm)
- NFV/ddI/ddT: 62 percent <50 copies/mL
- EFV/NVF/ddI/ddT: 62 percent <50 copies/mL

Efavirenz plus two NRTIs also did better than the NRTI-sparing regimen EFV/LPV/RTV in people with advanced disease who had responded to a three- or four-drug first-line PI or NNRTI [abstract 162]. The higher LPV/RTV dose needed with EFV (533/133 mg twice daily) caused more toxicity in that arm and probably contributed to its poorer performance.

Reporting for ACTG A5116 colleagues, Margaret Fischl (University of Miami) explained that everyone in the study had started a three- or four-drug medley with a CD4 count at or below 200 cells/mm³ and a viral load atop 80,000 copies/mL. They had no resistance to AZT, ddI, d4T, PIs, or NNRTIs, never had two consecutive blips or open the door to resistant virus. Instead, he confirmed that blips in viremia do not portend sustained viral rebounds or open the door to resistant virus.22 Instead, he concluded, blips probably reflect variation in hair-trigger replication-ready HIV species.21 The baseline viral population will not evolve at ongoing low-level replication (though this remains unproved) and one representing release of virus from a stable reservoir of about 1 million resting CD4 cells—a mere dewdrop in the body’s ocean of T lymphocytes [abstract 179]. When something pricks these cells into premeditated mode (it happens all the time), they spill virus back into circulation, where hawk-eyed handlers of supersensitive assays can count it.

Siliciano’s lab showed that this replication-ready HIV can drip back into circulation for years. But if a person is taking a potent regimen and keeps the viral load under 50 copies/mL, that virus will not mutate into resistant species. The baseline viral population will not evolve at all. Further work by his group published just before CROI confirmed that blips in viremia do not portend sustained rebounds or open the door to resistant virus. Instead, he concluded, blips probably reflect variation in hair-trigger RNA assays.

Scouring data from the Dutch ATHENA cohort, Irene van Valkengoed (HIV Monitoring Foundation, Amsterdam) found equivalent CD4, RNA, and progression trends in 87 blippers and 134 nonblippers tracked during

In a separate analysis of this trial, Pablo Tebas (Washington University, St. Louis) reported progressive limb fat loss in the EFV/NRTI group and a progressive gain in the NRTI-sparing arm [abstract 40]. But at what a price. Besides the higher risk of failure with EFV/LPV/RTV, people taking those drugs endured elevations of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Glucose and insulin rose in the EFV/NRTI group, but so moderately that Fischl discounted the clinical import of those gains.

Together these studies confirm the worth of plain old triple EFV therapy for people starting therapy or shifting from another suppressive regimen. Confirming these confirmations, John A. Bartlett (Duke University, Durham, North Carolina) decocted data from 49 clinical trials of triple regimens (counting a boosted PI as one drug) in people with little or no treatment experience [abstract 586].

Rating antiviral vim in 48-week intent-to-treat analyses, he found that 17 of the 21 combinations yielding the highest sub-50-copy rates consisted of one NNRTI and two NRTIs. Fourteen of those 17 winners included EFV—along with 3TC/abacavir (ABC) in four, ddT/3TC in three, AZT/3TC in two, ddI/3TC in two, ddI/emtricitabine (FTC) in two, and 3TC/tenofovir (TDF) in one. Ritonavir-boosted PI regimens did win this 49-study scrum by one criterion—best 48-week CD4 gains.

What goes on under the 50-copy cutoff?

When treatment pushes your viral load under 50 copies/mL, does it matter if you have 30 copies or 3? It’s hard to say, says Robert Siliciano (Johns Hopkins University, Baltimore), who has spent years finessing sub-50 findings.

Speaking in one of CROI’s last sessions, he defined two viral load strata under the 50-copy limit—one representing ongoing low-level replication (though this remains unproved) and one representing release of virus from a stable reservoir of about 1 million resting CD4 cells—a mere dewdrop in the body’s ocean of T lymphocytes [abstract 179]. When something pricks these cells into predatory mode (it happens all the time), they spill virus back into circulation, where hawk-eyed handlers of supersensitive assays can count it.
three years of ART [abstract 602]. Defining a blip as an RNA reading between 50 and 1,000 copies/mL after at least two loads below 50 copies/mL and followed by another under that mark, she estimated an overall blip rate of 6.3 per 100 person-years in 1,730 ATHENA members with more than one year of on-treatment follow-up. The blip rate rose from 2.9 per 100 person-years in the first year of treatment to 7.6 in the second, then settled back to 3.5 in the third.

The 87 blippers matched 134 no-blip controls in age, gender, HIV transmission group, time since HIV diagnosis, year of first treatment, drug levels, baseline CD4 and RNA levels, and baseline AIDS status. Through three years of follow-up, the median CD4 count rose from 140 to 430 cells/mm³ in the blip group and from 180 to 410 cells/mm³ in nonblippers. Three blippers (4 percent) and four controls (3 percent) had rebounds above 1,000 copies/mL. Eight blippers (9 percent) and 15 controls (11 percent) had a new AIDS diagnosis.

What separates people with loads bubbling under the 50-copy mark from those with the very lowest loads? Studying 145 responders in a trial comparing LPV/RTV with NFV, Sarah Palmer (National Cancer Institute, Frederick, Maryland) found only one discriminating factor: Lower pretreatment viral load correlated significantly (p < 0.001) with lower on-treatment viremia—gauged by an assay with a 1-copy limit—after 60 weeks of treatment [abstract 163]. She reckoned a viral load of about 3 copies/mL in both treatment arms.

Just after CROI a study using a 2.5-copy cutoff assay confirmed Palmer’s correlation between lower pretreatment viral load and lower sub-50 viremia. This analysis of 100 people in the trial comparing TDF with d4T (plus 3TC and EFV) also linked loads under 2.5 copies/mL with lower HIV DNA quotients in peripheral blood mononuclear cells and with TDF rather than d4T therapy. But how far below 50 the viral load went did not affect CD4 counts or the viral rebound risk through 72 weeks of follow-up.

Another try with triple nukes

Last year’s CROI confirmed the scalding failure of triple-NRTI amalgams lacking a thymidine analog (AZT or d4T). And AZT-containing Trizivir didn’t measure up to EFV combos in a big ACTG trial. So you would think the itch to try triple nukes had been well scratched.

Not at all. David Rey (Strasbourg University Hospital, Strasbourg, France) and confreres still have the yen to test an AZT/3TC combination—but this time with TDF instead of ABC—at least in a nonrandomized trial [abstract 599]. The rationale for this tactic rests on competing resistance pathways of AZT and TDF—mutations conferring resistance to these drugs almost never share a genome. Alone among licensed nucleosides, AZT retains activity against the TDF-provoked K65R mutant. And 24-week results from a trial of first-line once-daily Trizivir plus TDF showed a reasonable virologic response, though more people with a baseline load below 100,000 copies/mL (85 percent) than above that brink (61 percent) claimed fewer than 50 copies/mL at six months.

The Strasbourg study involved 42 treatment-naive people with a median CD4 count of 233 cells/mm³ (range 23 to 425 cells/mm³) and a median viral load of 4.88 logs (about 75,000 copies/mL). Over a median eight months of follow-up, nine people (21 percent) stopped the three NRTIs, four because of virologic failure and five because of side effects (including two cases of anemia). On-treatment genotyping of the four people with virologic failure showed only the K65R mutation in one, the AZT-evoked M41L and T215N mutations (detected before treatment) in another, and mixes of AZT mutations and the 3TC-disabling M184V in the others. The median CD4 count climbed 82 cells/mm³.

Rey did not break out results of the 19 people who started treatment with more than 100,000 copies/mL. The nonrandomized design of this pilot study makes it impossible to rate Combivir/TDF against sanctioned first-line remedies.

A nonrandomized trial in Uganda gave the same regimen to 200 adults with a median CD4 count of 100 cells/mm³ and a median viral load of 333,000 copies/mL [abstract 22]. After 24 weeks only 54 percent had a viral load under 50 copies/mL in a missing-data-equal-failure analysis.

Induction-maintenance redivivus

Induction-maintenance—another once-touted first-line tactic that fell by the wayside—also got a fresh look at CROI. Three early studies of this stratagem flopped, partly because both the induction and the maintenance regimens look substandard from today’s vantage.

But Diane Havlir (University of California, San Francisco), who headed one of those studies, argued at CROI that induction-maintenance deserves another go [abstract 181]. Eighteen-month follow-up of people in the French trial who stuck with their maintenance drugs despite their doctors’ advice, Havlir noted, showed that 14 of 17 taking only AZT/3TC and 14 of 15 taking AZT/IDV kept replication under wraps.

British researchers obliged Havlir’s zeal in a randomized trial of standard therapy (one NNRTI plus two NRTIs) versus 24 to 32 weeks of induction with one NNRTI, two NRTIs, and one PI [abstract 575]. People taking the quadruple induction combo could drop the PI if they had two consecutive RNA readings below 50 copies/mL after week 24 to 32. (True enough, this “maintenance regimen” is authorized as full-time therapy in current guidelines, but the value of four-drug induction still needs proving.) The induction-maintenance group ended up with a lower rate of virologic failure, but that result defies easy explanation.

Clive Loveday (International Clinical Virology Center, Buckinghamshire, UK) and colleagues randomized 122 people with an AIDS-defining median CD4 count of 160 cells/mm³ (IQR 90 to 260 cells/mm³) and a mean
starting viral load of 4.94 logs (about 87,000 copies/mL). The study group was largely male (88 percent) and gay (71 percent). More people started NVP (n = 77) than EFV (n = 44), and because the trial began in 1999 the most popular PI was NFV (in 44) followed distantly by LPV/RTV (in 17).

After a median 79.6 weeks of follow-up in the induction-maintenance group and 82 weeks in the control arm, rates of protocol-defined virologic failure proved significantly higher in the control group (Table 3).

In an analysis adjusted for baseline viral load and CD4 count, the risk of failure was two thirds lower in the induction-maintenance arm (HR 0.34, 95 percent CI 0.17 to 0.70).

Aside from the better outcome in the experimental group, the result that leaps out is the high virologic failure rate with standard NNRTI therapy. Yet although 43 percent looks like a high failure rate, it reflects 80 weeks of follow-up, not the 48 weeks reported for most studies. The under-50-copy rate for 48 weeks, 65 percent, is more in line with recent studies. As Loveday observed in a note to the IAPAC Monthly, the median 48-week NNRTI failure rate in a multistudy review presented at the conference looks like a high failure rate, it reflects 80 weeks of follow-up, not the 48 weeks reported for most studies. The under-50-copy rate for 48 weeks, 65 percent, is more in line with recent studies. As Loveday observed in a note to the IAPAC Monthly, the median 48-week NNRTI failure rate in a multistudy review presented at the conference measured 64 percent [abstract 586].

The data presented suggest no baseline imbalance between the induction-maintenance and standard-of-care arms: Rates of baseline resistance were similar in the two study groups, at about 15 percent. And early control of viremia does not explain the difference in virologic outcome: Intense viral load monitoring of 34 people in the first 15 days of therapy drew nearly superimposable RNA slopes in the two study groups. Further analysis of HIV-1 subtype and proviral DNA offered no hints toward explaining the difference in virologic failure.

The result may look surprising in that most trials comparing three-drug and four-drug first-line therapy saw no advantage with the extra drug through 48 weeks. In a report at the 5th Annual Workshop on Clinical Pharmacology of HIV Therapy, Andrew Hill (then at Roche) found only one in nine randomized trials that saw a virologic edge with quadruple therapy. Most recently, QUAD study researchers discovered that AZT/3TC/EFV did as well as AZT/3TC/ABC/EFV in people starting treatment with a six-figure viral load. But Loveday pointed out that QUAD and most of the studies reviewed by Hill combined four drugs from two classes, while his trial combined four drugs from three classes. And one of the four was a boosted PI—an ingredient not used in ACTG 384 or INITIO (see “Something not new...”, page 75). If others can confirm Loveday’s result, taking a boosted PI for the first eight months of treatment does not seem so onerous a burden when the reward is better long-term control.

### At last—a possible advantage of aging

The graying of the HIV population in lands of antiretroviral plenty raises questions about how older age may affect responses to first-line therapy. The answer from two US cohorts seems to be that people over 50 reap greater virologic rewards than younger folk [abstract 596]. And despite worries about waning T-cell output with age, the senior contingent gained CD4 cells as avidly as their juniors.

Kristine Patterson (University of North Carolina at Chapel Hill, USA) and colleagues at Johns Hopkins University in Baltimore ran a case-control comparison of people over or under 50 years old who started antiretrovirals with a potent regimen since January 1998. The 63 cases and 183 controls included 70 women and 176 men, two thirds of them black. About one in five picked up HIV by injecting drugs. The median age of cases stood at 54 years (IQR 51 to 60), compared with 38 years (IQR 32 to 48) in controls.

About half in each age group started a PI regimen and half started an NNRTI. Pretreatment CD4 counts were substantially higher in older women than in the other groups (Table 4). But equivalent proportions of the two age strata had a CD4 gain topping 25 percent through six months of follow-up, and equivalent proportions reached a viral load below 400 copies/mL (Table 4).

Despite the apparently equivalent six-month RNA response, the 50-plus caucus had an 80 percent better chance of reaching a sub-400 load compared with men under 50 in an analysis adjusted for study site, baseline viral load and CD4 count, and type of therapy (adjusted odds ratio [OR] for older women 1.8, 95 percent CI 0.5 to 6.4; adjusted OR for older men 1.8, 95 percent CI 0.8 to 3.9).

Patterson and colleagues don’t speculate on why the over-50 set harnessed viral replication better than the younger crowd. One might speculate that better adherence—begot by a keener appreciation of mortality among older people—could be a contributor. The higher CD4 count at diagnosis among older women may also reflect a greater concern for their own health. These researchers did not try to rate adherence. But a California group did test adherence in a randomized trial:

| Table 3. Failure with induction-maintenance versus standard therapy |
|-------------------|-------------------|-------------------|
| Induction-maintenance, n (%) | Standard therapy, n (%) | Total, n (%) |
| n | 62 | 60 | 122 |
| Not <50 copies/mL at week 32 | 7 (11) | 17 (28) | 24 (20) |
| <50 copies/mL at week 32, then >400 | 4 (6) | 9 (15) | 13 (11) |
| Total | 11 (18)† | 26 (43)† | 37 (30) |

*Standard therapy consisted of one NNRTI plus two NRTIs. Induction consisted of those drugs plus one PI, followed by NNRTI/2NRTI maintenance.

†p = 0.002.

Source: Clive Loveday, abstract 181.
Five lessons in better adherence

With clinicians at five southern California clinics, Glenn Wagner (Rand Corporation, Santa Monica, USA) randomized people starting, restarting, or switching antiretrovirals to one of two adherence plans or to “usual care” [abstract 614]. The adherence programs significantly improved pill taking compared with the control group, although that difference has not paid virologic dividends through 24 weeks of follow-up. The trial, which also includes a drug level monitoring component, will last 48 weeks.

Wagner offered a 24-week analysis of 199 people starting their first antiretrovirals and randomized to (1) pretreatment practice plus cognitive/behavioral intervention, (2) cognitive/behavioral intervention alone, or (3) usual care. (What is “cognitive/behavioral intervention”? Note 34 explains.) The adherence sessions came in five servings — three before therapy started and two afterwards. Pretreatment pill-taking practice added nothing to cognitive/behavioral training, so Wagner combined group one and two results in the comparison with group three.

The cohort was 50 percent Latino, 29 percent white, 13 percent black, and 20 percent female. Just over one third were employed, and 42 percent had no insurance. The mean starting CD4 count measured 188 cells/mm³ and the mean viral load 5.2 logs. An intention-to-treat analysis 24 weeks after treatment began documented much better adherence in the intervention groups, as measured by tattletale electronic bottle caps:

- At least 90 percent of doses taken: 82 percent versus 65 percent ($p=0.01$)
- Mean percent of doses taken at right time: 85 percent versus 79 percent ($p=0.07$)
- At least 90 percent of doses taken at right time: 57 percent versus 41 percent ($p=0.05$)

Despite better pill taking in the intervention group, viral load responses did not differ significantly from the control group at the study’s 24-week halfway point. For example, the average viral load dropped 2.15 logs in the intervention group versus 1.97 logs among controls. But adherence reckoned as percent of doses taken did correlate significantly with the 24-week viral load drop ($r = 0.2, p=0.03$).

**LIFE AND DEATH**

Dutch insurers made headlines just after CROI when they decided to write life policies for people with HIV—but only for those who pulled out of their CD4 nosedive with the help of antiretrovirals, who have no other life-threatening maladies, and who don’t inject drugs. Still, the shrewd underwriters’ estimate that they can make money betting on the lives of people with HIV as readily as those of people with heart disease or diabetes says something about the boons of ART.

Work detailed at the 12th CROI explained why life expectancy keeps climbing in the West, even as it crashes across Africa: Antiretroviral response rates mount with each passing year, according to a multicohort EuroCanadian study [abstract 593], while rates of triple-class failure fall [abstract 594].

But treatment has its limits. Three big studies agreed that scudding CD4 gains flatten out after three or four years of treatment—usually before scrabbling into normal territory [abstracts 609, 611, 612]. HIV death rates also stumbled into flatland after the big post-1995 plummet, at least at London’s Royal Free Hospital [abstract 957]. The overall risk of death among Norwegians with HIV quadruples the death risk of all Norwegians, but the risk of a non-HIV death is now lower in HIV-infected people [abstract 959].

Perhaps the most useful survival news came from the Vancouver group, who showed that pretreatment CD4 percent predicts survival even among British Columbians who start therapy with 200 to 350 cells/mm³ [abstract 589].

**Better response rates, fewer failures**

With confederates in Calgary, Barcelona, Nice, and Frankfurt, Fiona Lampe (Royal Free Hospital, London) charted at least a halving of the virologic failure rate among 4,143 adults who started antiretrovirals with a potent regimen from 1996 through 2002 (Table 5) [abstract 593]. The risk of gaining fewer than 50 CD4 cells/mm³ in the first year of treatment also dropped significantly.

Favored first regimens changed dramatically with time, with single PI combos plunging from 83 percent of all prescriptions in 1996 to 9 percent in 2002 while NNRTI medleys rose from 4 percent to 47 percent over those years and boosted PIs from 1 percent to 30 percent.
In the first three to four years of therapy, the overall median CD4 count rose from 210 cells/mm³ (IQR 91 to 355 cells/mm³) to 443 cells/mm³ (IQR 295 to 625 cells/mm³). So at the end of follow-up more than half of the cohort still had a count below 500 cells/mm³. After seven years of treatment, 41 percent inched across the 500-cell line.

Absolute CD4 gains looked similar in people who stayed with the same regimen and people who tried multiple combinations. But T-cell upticks proved significantly higher in people who never stopped their antiretrovirals than in those who took holidays. Kaufmann plotted a significant inverse correlation between the number and duration of antiretroviral breaks and CD4 jumps at seven years \( (r = -0.32, p < 0.001) \) for both correlations.

Angels Jaén (Center for Epidemiological Studies on HIV/AIDS, Badalona, Spain) and colleagues in 11 Spanish hospitals found that rising CD4 tallies pancaked after four years of potent therapy in everyone except those starting with fewer than 100 cells/mm³ \[abstract 611\]. This analysis of 1,452 people beginning treatment after 1997 also traced a significant correlation between starting CD4 tally and the last measured count \( (p < 0.001) \):

- Baseline 0-200: median last count 353 cells/mm³
- Baseline 201-350: median last count 527 cells/mm³
- Baseline 351-500: median last count 652 cells/mm³
- Baseline >500: median last count 777 cells/mm³

The AIDS rate during follow-up proved significantly higher in the lower baseline strata — 19.9 percent, 7.3 percent, 2.3 percent, and 2.5 percent \( (p < 0.001) \). But mortality did not differ significantly by starting CD4 count. People who entered the PISCIS cohort when older than 40 years and responded to treatment gained fewer CD4 cells than younger responders.

French APROCO cohort researchers sighted a T-cell tableland after three years of suppressive therapy in 1,281 people who started a PI regimen in 1997 or later \[abstract 612\]. But Lampe showed that this shift did not fully account for improving virologic trends, because the second adjusted risk ratio in Table 5 considers first-line drugs and still shows a year-after-year drop in risk of failure. So, Lampe ventured, “factors such as increases in adherence and improvements in clinical management . . . may have made an additional contribution.”

Nicholai Lohse (Odense University Hospital, Odense, Denmark) and colleagues across Denmark agreed that “better patient coaching” in recent years could explain better treatment responses, measured in this study as rates of triple-class failure \[abstract 594\]. Although this inquest involved only Danish people taking a potent regimen, it included 2,722 individuals — everyone cared for at a public HIV clinic.

Defining failure as a viral load above 1,000 copies/mL for 120 (not necessarily consecutive) days on a regimen, Lohse counted 177 three-class failures over a median 3.7 years of follow-up. The incidence of triple failure swelled in the first three years of therapy, then swooned significantly. From the third to sixth year of treatment, treble-class failures dropped 16 percent yearly \( (p = 0.04) \) including a 20 percent per annum plop among treatment-experienced people \( (p = 0.022) \).

Incidence of triple burnout peaked at 3.7 failures per 100 person-years in 2000, then fell to 1.6 per 100 person-years in 2001, 0.7 per 100 person-years in 2002, and 0.4 per 100 person-years in 2003. From 1997 through 2003 the incidence of triple failure skidded 12 percent yearly \( (p = 0.002) \).

### Table 5. RNA and CD4 failure risk at six clinics

<table>
<thead>
<tr>
<th>Year starting antiretrovirals</th>
<th>1996</th>
<th>1999</th>
<th>2002</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic failure (%) ( n=4,143 )</td>
<td>40.1</td>
<td>34.0</td>
<td>25.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Virologic failure (%) ( n=3,360 )</td>
<td>29.7</td>
<td>18.1</td>
<td>12.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Virologic failure (%) ( n=3,111 )</td>
<td>24.8</td>
<td>12.4</td>
<td>8.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted risk ratio ( M=F ) * for failure</td>
<td>1.41</td>
<td>1</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Adjusted risk ratio ( M=F ) ‡ for failure</td>
<td>1.27</td>
<td>1</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>&lt;500 cells/mm³ gain (%)</td>
<td>39</td>
<td>40</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Adjusted risk ratio ( M=F ) ‡ for CD4 failure</td>
<td>1.13</td>
<td>1</td>
<td>0.82</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M = F = missing-equals-failure analysis; exclude M = excluding missing data analysis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Adjusted for age, gender, risk group, pretreatment viral load and CD4 count, pretreatment AIDS.</td>
</tr>
<tr>
<td>‡Adjusted for above factors plus starting regimen.</td>
</tr>
<tr>
<td>†Adjusted for age, gender, risk group, pretreatment viral load and CD4 count, pretreatment AIDS.</td>
</tr>
<tr>
<td>M = F = missing-equals-failure analysis; exclude M = excluding missing data analysis.</td>
</tr>
<tr>
<td>Source: Fiona Lampe, abstract 593.</td>
</tr>
</tbody>
</table>

### A lifelong CD4 deficit?

The Swiss, the Spanish, and the French may not agree on cheese, chocolate, or the toughest climb in the Tour de France, but they agree that CD4 counts stop climbing after three or four years of potent therapy. Nationwide studies in all three countries logged muscle-popping T-cell ascents among virologic responders in the early years of treatment — followed by tabletop plateaus linked to starting CD4 counts.

The biggest and longest analysis came from Gilbert Kaufmann (University Hospital Basel, Switzerland) and the Swiss HIV Cohort Study, who tracked CD4 changes in 6,497 people for seven years or more \[abstract 612\]. The Swiss team divided their cohort into 2,449 people who never interrupted treatment (642 took only one regimen, 1,425 took several, and 400 took several highly active antiretroviral therapy (HAART) plus non-HAART regimens) and 4,048 who had breaks in their treatment (2,936 took only HAART and 1,112 also took a non-HAART regimen).

Across all these groups, the biggest CD4 gains came in the first three to four years of therapy. The overall median CD4 count rose from 210 cells/mm³ (IQR 91 to 355 cells/mm³) to 443 cells/mm³ (IQR 295 to 625 cells/mm³). So at the end of follow-up more than half of the cohort still had a count below 500 cells/mm³. After seven years of treatment, 41 percent inched across the 500-cell line.

Absolute CD4 gains looked similar in people who stayed with the same regimen and people who tried multiple combinations. But T-cell upticks proved significantly higher in people who never stopped their antiretrovirals than in those who took holidays. Kaufmann plotted a significant inverse correlation between the number and duration of antiretroviral breaks and CD4 jumps at seven years \( (r = -0.32, p < 0.001) \).
609]. After a median follow-up of 57 months, Vincent Le Moing (University Hospital of Montpellier, France) confirmed the Swiss and Spanish finding that people starting therapy at lower CD4 counts reached lower plateaus than those starting with more CD4 cells.

The overall upward CD4 slope measured 29.9 cells/mm³ monthly before month four, 6.4 cells/mm³ between months four and 36, and 0.6 cells/mm³ monthly after month 36. An unadjusted analysis picked out three factors that predicted a slow but steady CD4 gain after three years of treatment: male gender (+1 cell/mm³ monthly, \( p = 0.04 \)), treatment naive at baseline (+2 cells/mm³ monthly, \( p = 0.02 \)), and baseline CD4 count under 100 cells/mm³ (+2.6 cells/mm³ monthly, \( p < 0.01 \)). Variables that did not predict a growing CD4 quotient after 36 months were HIV transmission group, hepatitis C virus status, PI prescribed at baseline, and switch from a PI to a non-PI regimen.

An analysis adjusted for age, gender, baseline naive or AIDS status, and baseline CD4 and RNA found only two factors that foretold a positive CD4 slope from month four to month 36—age under 50 years (+2.84 cells/mm³ monthly, \( p = 0.02 \)), and baseline viral load above 100,000 copies/mL versus under 10,000 copies/mL (+2.77 cells/mm³ monthly, \( p = 0.001 \)).

**What is an “HIV-related death”?**

Three findings stand out in a mortality study by Caroline Sabin (Royal Free Hospital, London) [abstract 957]. First, the death rate at the Royal Free has been low but fairly flat since 1998. Second, deaths among just-diagnosed people do not explain this persisting mortality. And third, unlike other researchers Sabin did not chart a significant drop in the HIV-related death rate over time.

In a cohort that includes nearly 3,000 people since potent therapies arrived, Sabin plotted an 8.1 percent death rate in 1996, 4.0 percent in 1997, 1.8 percent in 1998, 1.8 percent in 1999, 2.1 percent in 2000, 1.0 percent in 2001, 0.9 percent in 2002, and 0.8 percent in 2003. So mortality measured about two deaths per 100 person-years in 1998 to 2000 and about one in 2001 to 2003. She attributed 52 percent of all deaths directly to HIV, and that quotient did not fall significantly after 1996 (\( p = 0.18 \)).

Of the 231 deaths chronicled, only 31 (13 percent) involved people diagnosed with HIV in the preceding six months, with no clear trend in that statistic over time. Almost everyone who died had low hemoglobin, and half had abnormal triglycerides or albumin.

The steadfast HIV-linked death rate in the Royal Free cohort prompted Sabin to call for closer scrutiny of other big data sets “to clarify how the classification of ‘HIV-related’ should be made in the HAART era.”

With Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study colleagues, Sabin tried to do just that by analyzing 1,248 deaths over 76,893 person-years of follow-up in this collaboration of European, US, and Australian researchers [abstract 595]. Reporting for the group, Rainer Weber (University Hospital, Zurich, Switzerland) made plain the difficulties in isolating HIV as the factor or a factor that leads to death.

Weber and colleagues grouped deaths into four clusters:

- HIV/AIDS-related (including HIV/AIDS, invasive bacterial infection, euthanasia)
- Liver-related (including chronic viral hepatitis and liver failure)
- Malignancy-related (including non-AIDS, non-hepatitis malignancies)
- Heart-related (including myocardial infarction and other cardiovascular or heart disease)

Even these broad groups have blurry lines between them, since liver failure can be an antiretroviral side effect, some “non-AIDS malignancies” may well belong on the AIDS list, and the D:A:D team itself demonstrated that more years of ART raise the myocardial infarction risk [abstract 42]. Weber’s findings tended to broaden the blur.

AIDS led this field of grim reapers, accounting for 30 percent of deaths, followed by liver failure (14 percent, nearly all due to hepatitis), heart disease (9 percent), and “non-AIDS malignancies” (8 percent). Minor contributors to the death rolls (at rates between 2 percent and 5 percent) included other problems familiar to HIV clinicians—suicide, pancreatitis, lactic acidosis, and renal failure.

As D:A:D workers anticipated, HIV/AIDS deaths correlated strongly with CD4 count, at an adjusted relative rate of 96.4 with a count below 50 cells/mm³ versus above 500 cells/mm³ (\( p < 0.0001 \)). But the risk of death from liver failure and “non-AIDS malignancies” also rose significantly with a sub-50 CD4 count—at a relative rate of 26.6 for liver deaths and 23.5 for malignancies (\( p < 0.0001 \) for both).

Weber and coworkers proposed that deaths at very low CD4 counts “can only be categorized as non-HIV-related if there is clear evidence that the patient’s immunodeficiency did not contribute to death.” Indeed, these findings led D:A:D to toss out its mortality code and build a new one with a sharper focus on immunodeficiency.

In Norway the overall five-year risk of death among people with HIV compared with the general population fell by almost 85 percent after the dawn of brawny therapies [abstract 959]. And the risk of a non-HIV death proved lower after 1995 in the HIV cohort than among all Norwegians.

Vidar Ormaasen (Ullevål University Hospital, Oslo, Norway) and colleagues at Akershus University Hospital in Lørenskog, Norway reckoned death rates in 782 people seen from January 1982 through December 1994 and in 398 seen from January 1997 through March 2004. Compared with the general population, the death risk ratio for the pre-1995 group measured 22.6 (95 percent CI 19.5 to 26.4) and for the post-1995 group 3.96 (95 percent CI 2.25 to 6.67).
The risk ratio for non-HIV-related deaths in the pre-1995 group measured 3.70 (95 percent CI 2.60 to 5.25) compared with Norwegians at large, and 0.61 (95 percent CI 0.15 to 2.44) in the post-1995 group. In other words, Norwegians treated for HIV infection since 1997 had about a 40 percent lower risk of a non-HIV death than did the general population. And when Ormaasen eliminated injecting drug users from the analysis, the pre-1995 group no longer had a higher risk of a non-HIV death than the overall population.

**Forget baseline count, try CD4 percent?**

Work by the Vancouver group found CD4 percent a strong predictor of survival among people starting a robust regimen after mid-1996 [abstract 589]. David Moore (British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada) also showed that CD4 percent remains a reliable harbinger of death among people who fall into the CD4 count gray zone of 200 to 350 cells/mm³ before starting therapy.

The larger analysis involved 1,623 people starting their first antiretrovirals in August 1996 or later and followed until death or June 30, 2003. In a multivariate analysis adjusted for age, adherence, initial viral load, and pre-treatment AIDS diagnosis, Moore isolated six factors that foretold a higher risk of nonaccidental death:

- CD4 percent <5 (versus ≥15): Relative risk [RR] 4.46 (95 percent CI 2.92 to 6.79)
- CD4 percent 5 to 14 (versus ≥15): RR 2.42 (95 percent CI 1.75 to 3.38)
- Older age (per year): RR 1.04 (95 percent CI 1.03 to 1.06)
- AIDS diagnosis: RR 5.15 (95 percent CI 1.87 to 14.14)
- Baseline RNA ≥100,000 copies/mL: RR 3.48 (95 percent CI 1.54 to 7.79)
- Adherence (in 10 percent decrements): RR 1.14 (95 percent CI 1.04 to 1.24)

Then Moore focused on 417 people who began treatment without AIDS and with a CD4 count between 200 and 350 cells/mm³. In this subgroup three independent predictors of nonaccidental death emerged:

- CD4 percent <15 (versus ≥15): RR 2.71 (95 percent CI 1.20 to 6.10)
- Adherence (in 10 percent decrements): RR 1.18 (95 percent CI 1.05 to 1.33)
- Baseline RNA ≥100,000 copies/mL: RR 2.57 (95 percent CI 1.00 to 6.58)

Moore and coworkers suggested that CD4 percent “should be considered for inclusion in therapeutic guidelines to determine when to start therapy.” It may also add more evidence when making tough individual calls about when to start.

**Missed opportunities for diagnosing HIV**

One doesn’t need an advanced degree in statistics, or even a fancy calculator, to cite one immutable death predictor in people with HIV — getting treated late, or not at all. Yet US clinicians routinely miss HIV diagnoses, according to one CROI study. Edward Gardner (Denver Public Health Department, Denver, USA) figured that one third of people with HIV newly diagnosed in the Denver Health system received care there within the preceding three years, and more than a few had problems hinting at HIV [abstract 966].

The Denver Health population reflects poor and underserved groups in many US cities. Area residents without insurance typically use Denver Health as their sole source of care, often showing up at the emergency room or urgent care clinic. Gardner underlined the key limitation of this retrospective analysis — the inability to establish when people newly diagnosed with HIV actually became infected. So there may have been few clues of HIV when they made earlier visits. But in some cases the clues seemed clear.

Gardner ran a case-control comparison of 120 just-diagnosed people who came to Denver Health in the preceding three years and 228 just-diagnosed controls without an earlier visit. The cases included more females (22 percent versus 10 percent, p = 0.001) and had a lower median CD4 count at diagnosis (370 versus 458 cells/mm³, p = 0.01) and a higher viral load (4.7 versus 4.5 logs, p = 0.06). The case group also included more Hispanics (37 percent versus 19 percent) and more primary Spanish speakers (17 percent versus 11 percent), but those differences lacked statistical significance.

Among people who sought care at Denver Health in the preceding three years, most visits involved the urgent care clinic (58 percent) or the emergency room (50 percent), though 29 percent of visits were in primary care offices and 16 percent after hospital admission. Thirty-four of the 120 cases (26 percent) had made five earlier visits.

At least 18 cases (15 percent) had a clinical indicator of HIV at their earlier visit, though six of those 18 refused an HIV test at the time. Twenty-eight cases (23 percent) had an earlier respiratory infection, 19 (16 percent) had an earlier sexually transmitted disease (STD), and 13 (11 percent) had an earlier skin infection. Workers in the STD clinic eventually made most of the HIV diagnoses. Diagnosis with a CD4 count below 200 cells/mm³ proved more common among older people and among Spanish speakers. Gardner also stressed the missed opportunities for spotting HIV among women and people with multiple infections.

**HEPATITIS COINFECTION**

The growing number of reports on hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection at CROI mirror growing concern over liver-related morbidity as people taking antiretrovirals skirt the dangers of more
exotic opportunists. Attendees at this year’s conference saw disturbing signals that HCV-provoked liver fibrosis may get worse faster in HIV-infected people than most anticipate. Research on entecavir—a novel anti-HBV drug just recommended for approval in the United States—showed that the drug does well in people already taking 3TC. And TDF looked good in a comparison with adeovir among HBV/HIV-coinfected people.

Risk of fast progression from mild fibrosis

When liver biopsy shows little or no fibrosis, physicians tell people with HCV they can delay treating this slowly progressive disease—perhaps until more potent and tolerable drugs arrive. But that advice may not work for some people coinfected with HIV, reported Mark Sulkowski (Johns Hopkins University, Baltimore) [abstract 121]. He found that more than one quarter of coinfected people with little or no fibrosis on their first biopsy had a two-stage jump in fibrosis on a biopsy three years later.

Sulkowski’s group pinched liver samples from 61 HCV/HIV-coinfected people twice over a median of 2.84 years (IQR 2.05 to 3.41 years). The same pathologist blinded to the biopsy sequence rated them on the Ishak scale, which scores no fibrosis 0, some portal area fibrosis 1, most portal areas with fibrosis 2, occasional portal-to-portal bridging fibrosis 3, and marked bridging fibrosis 4. The analysis eliminated people with a 5 or 6 score indicating cirrhosis on their first biopsy.

The 61 study participants had a median 23.8-year duration of HCV infection and a median age of 44 years at their first biopsy. While 21 percent had fewer than 200 CD4 cells/mm³ at that time, 57 percent had a viral load under 400 copies/mL and 82 percent had taken ART.

From the first to the second biopsy, 13 percent had a one-stage jump in fibrosis grade, 13 percent a two-stage jump, and 14 percent a three-stage jump. Among those who got a 0 or 1 score on their first biopsy, 28 percent had at least a two-stage vault on their second. Sulkowski found only one significant difference between people with at least a two-stage change and people with no change: 43 percent of fast progressors versus 17 percent of nonprogressors had an alanine aminotransferase (ALT) change: 43 percent of fast progressors versus 17 percent of nonprogressors had at least a two-stage change and people with no change.

Sulkowski called for more research to pinpoint predictors of faster fibrosis progression in coinfected people.

Until such predictors emerge, he proposed repeating a biopsy every three years in coinfected people with no or mild fibrosis.

A noninvasive gauge of liver fibrosis emerged from analysis of 832 coinfected people enrolled in the AIDS PEGASYS Ribavirin International Coinfection (APRICOT) trial of pegylated interferon. If validated, the FIB-4 score could allow coinfected people to make informed decisions on ART without facing biopsy’s big needle, proposed Richard Sterling (Virginia Commonwealth University, Richmond, USA) [abstract 120].

The APRICOT team split study participants into 555 for a “training set” to figure out the best noninvasive score and 277 for a “validation set” to test the candidate score. Using the Ishak fibrosis system they made three fibrosis groups: no or mild fibrosis (grade 0 to 1), moderate fibrosis (grade 2 to 3), or advanced fibrosis (grade 4 to 6). Picking out salient variables in univariate then multivariate analyses, Sterling settled on the following fibrosis formula:

\[
FIB-4 = \frac{\text{age} \times \sqrt{\text{ALT}}}{\text{AST} \times \text{PLT}}
\]

where AST is aspartate aminotransferase and PLT is platelets.

Nimble arithmeticians figured that a FIB-4 score of 1.45 or less had a 70 percent sensitivity, 74 percent specificity, 42 percent positive predictive value, and 90 percent negative predictive value for distinguishing between advanced (grade 4 to 6) and mild to moderate (grade 0 to 3) fibrosis. An upper cutoff of 3.25 had a 22 percent sensitivity, 97 percent specificity, 65 percent positive predictive value, and 82 percent negative predictive value for making the same split.

Applying these cutoffs to the 277-person validation set, Sterling reckoned the score would correctly rate fibrosis in 172 of 198 people (87 percent) whose FIB-4 fell outside the cutoffs. For those comfortable with 87 percent accuracy, that means 198 of 277 people (71 percent) could avoid liver biopsy.

Sherri Stuver (Boston University) and colleagues at other Boston sites relied on more familiar methods to predict liver disease progression in an urban coinfected cohort of injecting drug users—weighing viral and nonviral variables in people who do or do not have progressive disease [abstract 947]. The cohort included 231 coinfected people, 70 percent of them men, 51 percent black, 27 percent white, and 21 percent Hispanic. Most cohort members, 88 percent, had injected drugs at some point, 29 percent were injecting during this prospective study, and 21 percent drank alcohol to excess.

Twenty-two coinfected people endured a new liver-related setback or died to yield a progression rate of 5.1 per 100 person-years. In a univariate analysis, being Hispanic raised the progression risk 5.2 times (95 percent CI 1.1 to 24.3) and having a CD4 nadir below 100 cells/mm³ raised the risk 15.8 times (95 percent CI 2.0 to 122). On the other hand, reaching a viral load below 75 copies/mL
with antiretrovirals clipped the progression risk 71 percent (HR 0.29, 95 percent CI 0.08 to 1.00). Being black, having a CD4 nadir between 100 and 199 cells/mm³, and currently injecting drugs also raised the risk of progression, but not significantly. Neither dangerous drinking nor age at HCV or HBV infection boosted progression risk.

In a multivariate analysis, nadir CD4 count remained an independent predictor of liver disease progression:

- Nadir <100 (versus 300+) cells/mm³: HR 19.1 (95 percent CI 2.1 to 177)
- Nadir 100 to 199 (versus 300+) cells/mm³: HR 10.9 (95 percent CI 1.2 to 101)

Taking antiretrovirals and being black or Hispanic were marginal progression predictors in the multivariate analysis.

**Entecavir or TDF for HBV**

Not long after CROI the US Food and Drug Administration’s (FDA) advisory panel gave its blessing to entecavir for treating HBV infection. Although animal studies raised the specter of a cancer risk with entecavir, the panel decided that the drug’s potential benefit outweighs this possible risk and did not propose trumpeting the cancer findings in a “black box” warning. But the FDA, burned more than once in recent months by surprise side effects of approved blockbuster drugs, asked for further study of the cancer risk in people taking entecavir.

The new antiviral won the FDA advisors’ sanction by bettering 3TC in a randomized trial. With HBV resistance to 3TC rife among HIV/HBV-coinfected people, does entecavir do when the retrovirus and the hepatitis virus team up? The answer means a lot to coinfected people because entecavir has no anti-HIV activity and so does not select HIV-resistant virus. The drug’s potential for interacting with antiretrovirals also appears to be low. Speaking for colleagues running a phase 2 international trial of entecavir in coinfected people, Mario Pessoa (Infectious Disease Institute, São Paulo, Brazil) reported that adding the drug to a regimen swiftly lowers HBV load and sometimes brings ALTs back to normal [abstract 123].

The ongoing trial randomized 51 people to add 1 mg of entecavir once daily to a regimen containing 150 or 300 mg of 3TC and 17 people to add placebo. Everyone had compensated liver disease and an ALT at or below 10 times the upper limit of normal at screening. The average baseline HBV DNA load stood at 9.1 log copies/mL, and the average HIV RNA load under 200 copies/mL.

At week 24 the mean HBV load fell 3.66 logs with entecavir versus 0.11 log with placebo. After 24 weeks of treatment, 84 percent taking entecavir and no one taking placebo had an HBV load below 400 copies/mL or at least a 2-log drop. At the same point 46 percent in the entecavir group and 17 percent on placebo reached an ALT under 1.25 times the upper limit of normal. Alanine aminotransferase levels fell to the upper limit of normal in 34 percent taking entecavir and 8 percent taking placebo ($p=0.08$).

Nobody quit entecavir because of side effects, and only one person had a serious complication—hepatic encephalopathy and esophageal varices judged unrelated to therapy. Five people (10 percent) in the entecavir group had grade 3 or 4 treatment-related problems. The drug’s most common side effects in general population trials are headache, fatigue, diarrhea, and upset stomach.

The antiretroviral TDF also controls HBV replication, though it lacks an indication for anti-HBV therapy. Adefovir, TDF’s nucleotide cousin, flunked its antiviral exam but won an anti HBV license at a dose of 10 mg daily. Plenty of clinicians already giving TDF to HBV/HIV-coinfected people found reassurance in the CROI report that the drug does at least as well as adefovir in coinfected people—maybe better.

A trial enrolling coinfected people randomized 25 to take adefovir (plus TDF placebo) and 27 to take 300 mg of TDF daily (plus adefovir placebo) [abstract 124]. About three quarters of both groups had an HIV load under 400 copies/mL, and median CD4 quotients stood in the 400s. Everyone continued their antiretroviral regimen during the study. Marion Peters (University of California, San Francisco) reported starting mean HBV loads of 9.5 logs in the TDF group and 8.8 logs with adefovir. Most people in both groups had 3TC experience—an important point since both drugs control 3TC-resistant virus.

Peters and ACTG colleagues planned the trial to demonstrate the “noninferiority” of TDF to adefovir. After 52 people had taken the drugs for a median of 75 weeks, the trial’s independent panel decided it had seen enough to rank TDF as a noninferior agent, so it stopped the study. Because of that early closure, though, statisticians could not establish TDF’s superiority to adefovir, even though it bettered adefovir by about 1 log in lowering HBV load in two 48-week intention-to-treat analyses and the on-treatment analysis.

Hepatitis B virus loads dropped smartly with both drugs through the first 12 weeks of treatment. But HBV copies kept dwindling in the TDF arm through 60 weeks of follow-up, while declines leveled out in the adefovir arm. Yet the confidence intervals surrounding the means for each drug in that analysis overlapped, so Peters could not call TDF the better drug. The crucial analysis of people who began TDF or adefovir with 3TC-resistant virus was not finished when Peters spoke. Side effect rates did not differ much between treatment arms.

Mark Mascolini writes about HIV infection (markmascolini@earthlink.net).
15. Deeks SG, Grant RM, Wrin T, et al. Spectrum of antiretroviral use in the treatment of

References and Notes

2. The Power 1 and 2 cohort was predominantly male (89 percent) and white (74 percent), with an average age of 44 years. Mean duration of HIV infection averaged 12 years in the TMC114 group and 13 years in the control arm.
3. The 21 mutations that may figure in a resistance score for TPV riggeir protease at 16 positions: 10V, 12V, 20MVR, 35F, 35G, 41T, 46V, 47V, 54A, 54VR, 58E, 69K, 74F, 82U, 83D, and 84V.
34. Zhou J,买家S, Santoro G, et al. Components of cognitive/behavioral intervention in this study were (1) providing education about the importance of treatment, (2) skill building to identify and overcome barriers to adherence via pretreatment practice or mental rehearsal, (3) enhancing social support for treatment and adherence, (4) tailoring the regimen to the patient's daily schedule, (5) bolstering side effect management skills, and (6) increasing commitment and motivation to adhere over the long term.
Sexual HCV transmission among HIV-negative gay men

Michael Carter

Sexual transmission of hepatitis C virus (HCV) between HIV-negative gay men is extremely rare, according to a Canadian study published in the March 2005 edition of the American Journal of Public Health. In an eight-month period, only one incidence of HCV seroconversion occurred in a cohort of more than 1,000 gay men, and this case involved an individual who reported sharing injecting equipment in the previous six months.

There is considerable debate about the frequency of sexual HCV transmission, with epidemiological studies providing conflicting data. Studies in gay men have found a prevalence of HCV antibodies ranging from 1 percent in Denmark to 7 percent in Italy. Recent studies have suggested an increased prevalence and incidence of HCV coinfection in HIV-positive gay men, and it has been suggested that unprotected anal sex and fisting may be sexual activities which involve a significant risk of HCV transmission in this population.

In light of the conflicting data, investigators in Montreal examined the sexual transmission of HCV in a cohort of 1,054 gay men. This is the largest cohort of gay men in which the sexual transmission of HCV has been examined. These men were enrolled in the Omega Cohort Study, an ongoing prospective cohort into the risk factors of HIV transmission among gay men in Montreal. Enrollment started in 1996 and its objectives are to characterize changes in gay men’s sexual behavior and to identify the psychological factors associated with sexual risk taking.

Men enrolled in the study provided a blood sample on entry to the study and then at intervals of six months. Between January 2001 and September 2001, 1,085 men provided consent to enter a substudy, and for their blood samples to be tested for HCV antibodies. If the result was positive, and the sample obtained on entry to the substudy was also positive, the individual was excluded from the incident study. However, if the baseline sample was HCV antibody negative, all serum samples obtained since the individual enrolled in the Omega Study were tested to determine the probable date of HCV seroconversion. All men completed a detailed questionnaire enquiring about sexual activity and possible routes of HCV transmission.

Median age was 32 years, and the men in the study had extensive sexual experience. In total, 92 percent of men reported anal sex at some time with either a regular or casual partner, and 63 percent of men said that they had had unprotected anal sex with either a regular or casual partner. More than 40 percent of men said that they had had 50 or more sexual partners in their lifetime, and 37 percent said that they had had unprotected anal sex with a casual partner. In addition, 44 percent of men said that they had had five or more regular partners in their lifetime and 56 percent said that they had had unprotected anal sex with a regular partner.

Of the 1,085 men who participated in the study, 32 were HCV-positive (3 percent). Of these, it was found that 31 were already infected at baseline. The remaining individual seroconverted between the first and second follow-up visits. When the investigators looked at the HCV-risk activities of the 31 men who had antibodies to the virus at baseline, they found that 20 were current injecting drug users (IDUs), eight were former IDUs, and three had no reported history of injecting drug use. Therefore, HCV prevalence among the 980 gay men in the study with no reported history of injecting drug use was 0.3 percent.

Hepatitis C virus prevalence was much higher among current IDUs (48 percent) than former IDUs (20 percent, p = 0.006), and unsurprisingly was also higher among drug users who reported sharing needles than those who had never shared needles (48 percent versus 13 percent, p = 0.002).

After controlling for injecting drug use, sexual behavior was not significantly associated with prevalent HCV infection. The investigators examined in more detail the sexual behavior of the three non-IDUs with HCV. They found that their sexual behavior did not differ significantly from HCV-negative men. Indeed, two of the three men said that they had used condoms 100 percent of the time. One man said he had had a blood transfusion and a body piercing, and the other two reported cocaine snorting and body piercing.

According to the investigators, “the 1,085 men who were [HCV]-negative at baseline contributed a total of 2,653 person-years of follow-up. With only one seroconversion, the overall incidence of [HCV] seroconversion was 0.038 per 100 person years.”

Regarding this single seroconversion, the investigators note, “this seroconversion occurred in an [IDU] who reported needle sharing during the six months preceding the visit at which he first tested positive for [HCV].”

Reference

AIDS

The effect of baseline CD4 cell count and HIV-1 viral load on the efficacy and safety of nevirapine- or efavirenz-based first-line HAART

van Leth F, Andrews S, Grinsztejn B et al. for the 2NN Study Group.

BACKGROUND: A substantial number of patients start their first-line antiretroviral therapy at an advanced stage of an HIV-1 infection. Potential differences between specific drug regimens in antiviral efficacy and safety in these patients are of major importance. METHODS: A post hoc analysis within the randomized controlled 2NN trial comparing efficacy between regimes containing nevirapine (NVP), efavirenz (EFV), or both, in addition to stavudine and lamivudine. Primary outcome: risk of virologic failure in different strata of baseline CD4 T-lymphocyte counts and plasma HIV-1 RNA concentrations (pVL), Virologic failure: never reaching a pVL < 400 copies/mL, or a rebound to two consecutive values >400 copies/mL. RESULTS: The risk of virologic failure was increased at very low CD4 counts (<25 x 10⁶ cells/l) compared to CD4 counts >200 x 10⁶ cells/l (hazard ratio [HR], 1.28; 95 percent confidence interval [CI], 0.93-1.77). The same was seen for a pVL ≥100,000 copies/mL compared to a lower pVL (HR, 1.20; CI 0.96-1.50). There were no statistically significant differences between NVP and EFV in risk of virologic failure within any of the CD4 or pVL strata, although EFV performed slightly better in the low CD4 stratum. The incidence of rash in the NVP group was significantly higher in female patients with higher CD4 cell counts, while adverse events in the EFV group were not associated with CD4 cell count. CONCLUSIONS: Initial antiretroviral therapy including NVP or EFV is effective in patients with an advanced HIV-1 infection. A high baseline CD4 cell count is associated with the occurrence of rash in female patients using NVP.


Clinical Infectious Diseases

Hepatitis C virus coinfection and HIV load, CD4 cell percentage, and clinical progression to AIDS or death among HIV-infected women: Women and Infants Transmission Study


BACKGROUND: Despite previous study, it remains unclear whether hepatitis C virus (HCV) coinfection affects the progression of human immunodeficiency virus (HIV) type 1 infection. The Women and Infants Transmission Study provided an opportunity to assess this issue. METHODS: Longitudinal data on 652 HIV-1-infected women enrolled in the study before the availability of highly active antiretroviral therapy (HAART; 1989-1995) were analyzed. Random effects models were used to determine whether HCV coinfection was associated with different CD4 cell percentages and HIV-1 RNA levels over time, and Cox proportional hazards models were used to compare the rates of clinical progression to acquired immunodeficiency syndrome (AIDS) or death. RESULTS: Of 652 women, 190 (29 percent) were HCV-infected. During follow-up, 19 percent of women were exposed to HAART. After controlling for indicators of disease progression (CD4 cell percentages and HIV-1 RNA levels determined closest to the time of delivery in pregnant women), ongoing drug use, receipt of antiretroviral therapy, and other important covariates, no differences were detected in the HIV-1 RNA levels, but the CD4 cell percentages were slightly higher in HCV-infected women than in HCV-uninfected women. During follow-up, 48 women had progression to a first clinical AIDS-defining illness (ADI), and 26 died with no documented antecedent ADI. In multivariable analyses, HCV-infected participants did not have faster progression to a first class C AIDS-defining event or death (relative hazard, 0.75; 95 percent confidence interval, 0.37-1.53). CONCLUSIONS: In this cohort, the rate of clinical progression of HIV-1 infection was not greater for HCV-infected women.


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Sexually Transmitted Diseases

Designing equitable antiretroviral allocation strategies in resource-constrained countries

Wilson DP, Blower SM.

BACKGROUND: Recently, a global commitment has been made to expand access to antiretrovirals (ARVs) in the developing world. However, in many resource-constrained countries the number of individuals infected with HIV in need of treatment will far exceed the supply of ARVs, and only a limited number of healthcare facilities (HCFs) will be available for ARV distribution. Deciding how to allocate the limited supply of ARVs among HCFs will be extremely difficult. Resource allocation decisions can be made on the basis of many epidemiological, ethical, or preferential treatment priority criteria. METHODS AND FINDINGS: Here we use operations research techniques, and we show how to determine the optimal strategy for allocating ARVs among HCFs in order to satisfy the equitable criterion that each individual infected with HIV has an equal chance of receiving ARVs. We present a novel spatial mathematical model that includes heterogeneity in treatment accessibility. We show how to use our theoretical framework, in conjunction with an equity objective function, to determine an optimal equitable allocation strategy (OEAS) for ARVs in resource-constrained regions. Our equity objective function enables us to apply the egalitarian principle of equity with respect to access to healthcare. We use data from the detailed ARV rollout plan designed by the government of South Africa to determine an OEAS for the province of KwaZulu-Natal. We determine the OEAS for KwaZulu-Natal, and we then compare this OEAS with two other ARV allocation strategies: (i) allocating ARVs only to Durban (the largest urban city in KwaZulu-Natal province) and (ii) allocating ARVs equally to all available HCFs. In addition, we compare the OEAS to the current allocation plan of the South African government (which is based upon allocating ARVs to 17 HCFs). We show that our OEAS significantly improves equity in treatment accessibility in comparison with these three ARV allocation strategies. We also quantify how the size of the catchment region surrounding each HCF, and the number of HCFs utilized for ARV distribution, alters the OEAS and the probability of achieving equity in treatment accessibility. We calculate that in order to achieve the greatest degree of treatment equity for individuals with HIV in KwaZulu-Natal, the ARVs should be allocated to 54 HCFs and each HCF should serve a catchment region of 40 to 60 km. CONCLUSION: Our OEAS would substantially improve equity in treatment accessibility in comparison with other allocation strategies. Furthermore, our OEAS is extremely different from the currently planned strategy. We suggest that our novel methodology be used to design optimal ARV allocation strategies for resource-constrained countries.


ABSTRACTS
Iurie Climasevschi

For more than three 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 Iurie Climasevschi, Chief of Department of the Republican Dermatovenerologic Dispensary, Infectious Diseases/AIDS Department, in Chisinau, Moldova.

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it?
Never avoid difficulties, but find ways to solve them.

What activities, avocations, or hobbies interest you?
Sports and traveling.

If you could live anywhere in the world, where would it be?
In the United States, because there are perfect conditions for the activity of the physician.

Who are your mentors or real life heroes?
Otilia Benea, a physician at the Matei Bals Infectious Diseases Hospital in Bucharest, Romania.

With what historical figure do you most identify?
Napoleon.

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?
In the first half of the 20th century.

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

In your opinion, what are the greatest achievements and failures of humanity?
The greatest achievement: Victory in World War II. The greatest failure: The October Revolution of 1917 in Russia.

What is your prediction as to the future of our planet one full decade from present day?
Destruction of international terrorism; economic growth of the Third World; admission of Moldova to the European Union; creation of an anti-HIV vaccine.
In the current demographic situation it has become a question of strategic, social, and economic security.

Russian Deputy Prime Minister Alexander Zhukov quoted in a March 30, 2005, Agence France Presse report in which he commented on the Ministries of Health’s announcement that Russia has reduced the per-patient annual cost of antiretroviral drugs from US$10,000 to US$3,000, with the intention of further reducing annual costs to between US$1,400 and US$1,700. The reductions were achieved through negotiations with pharmaceutical companies. Experts have warned that the Russian epidemic is in its early stages, and that, if not addressed, the number of HIV-infected Russians could total 5.4 million by 2020.

One of the things that’s tough about tracking this disease and current infection patterns is knowing that test results don’t show what the infection rate is.

Julie Willems Van Dijk, health officer of Marathon County, Wisconsin, in a March 21, 2005, article published in the Wausau Daily Herald. The Wisconsin Division of Public Health reported an increase of 15 percent in new HIV infections for 2004, and a 35 percent increase over the last four years. Marathon is a rural county, and though rural counties have a smaller proportion of HIV-positive patients than do urban counties, their increase in new infections can be significant. Increases in other new sexually transmitted infections (eg, chlamydia, gonorrhea) have also been substantial and could possibly indicate increased high-risk sexual behavior.

I’m pretty much scared that we’re sitting on a ticking time bomb.

Ehab El Kharrat, Director of Freedom, a Presbyterian organization located near Cairo’s main train station that reaches out to drug users, in a March 13, 2005, Pittsburgh Post-Gazette article entitled, “Needle Sharing by Drug Users a Dangerous Sign.” El Kharrat, who has treated Cairo drug users for 16 years, did not know that many of his clients were sharing needles until he recently began discussing HIV awareness with them. Syringes and needles are inexpensive and available without a prescription in Egypt’s pharmacies. In speaking to his clients, however, El Kharrat discovered a superstition among users that getting new needles jinxes the chance of accessing more drugs.

Nigeria is facing a potentially catastrophic HIV/AIDS epidemic and suffers from serious malaria and TB epidemics. In light of its problems at home, the Nigerian contribution is a great act of global solidarity.

Richard Feachem, Executive Director of the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund), discussing a pledge of US$10 million made by Nigeria to the Global Fund, in a March 15, 2005, story reported on BuaNews/AllAfrica.com. Nigeria previously contributed US$10 million in 2002, and has thus far received US$201 million in funds from the Global Fund. Feachem added that Nigeria’s gesture should inspire more affluent donors to increase their contributions to the Global Fund.

Do you keep off of your committee every great expert out there because they can’t have a single penny from [the US National Institutes of Health] or do you strive for a balance, keeping any possible connection like that to an absolute best possible minimum?

Institute of Medicine (IOM) spokesperson Christine Stencel responding in a March 17, 2005, Associated Press report to concerns raised about a panel of nine researchers investigating HIVNET 012—a US National Institutes of Health (NIH)-funded, Uganda-based study of single-dose nevirapine use for the prevention of mother-to-child transmission of HIV. According to the Associated Press, six of the HIVNET 012 researchers annually receive between US$120,000 and US$2 million from the NIH, which is the subject of the IOM probe. Several members of the US Congress have expressed concern that the researchers’ financial ties to the NIH will cause their conclusions to be viewed skeptically.

To guarantee the sustainability of our [AIDS] program, we need to produce these drugs ourselves.

Jarbas Barbosa, a Brazilian Ministry of Health official, in a March 16, 2005, Associated Press report regarding that country’s request that three US-based pharmaceutical companies grant voluntary licensing of their products so that the country can cut healthcare costs. The government wants rights to four antiretroviral drugs—Merck’s efavirenz, Abbott’s lopinavir and ritonavir, and Gilead’s tenofovir—so that it can legally manufacture and distribute generic copies in support of Brazil’s antiretroviral therapy program.
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