Epidemic (and lesser) lessons from Rio Centro
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Mark Mascolini

The 3rd IAS Conference on HIV Pathogenesis and Treatment featured much more news than usual on HIV and antiretroviral therapy below the Tropic of Cancer. But HIV specialists from more boreal climes also got plenty to ponder—including the merits of tenofovir/emtricitabine, the pluses and minuses of thymidine versus nonthymidine nucleosides, and a growing load of growth hormone research.

Crystal methamphetamine use and antiretroviral drug resistance: A pilot study of behavioral and clinical correlates

Mark Mascolini
Progressive realization, interrupted

José M. Zuniga

icking off an already tumultuous tenure as US Ambassador to the United Nations (UN), outspoken UN critic John Bolton provoked an uproar by proposing an encyclopedic 750 changes to a draft “Outcomes Document” which outlined the goals and scope of the 2005 World Summit held September 14-16, 2005, in New York. This document—a third draft of which was released August 5, 2005—was intended as the final draft version and basis for agreement at the summit, which commemorated the UN’s 60th anniversary. However, in advance of the summit the United States indicated that it was unwilling to sign a document length of the draft, and one that it could not negotiate line by line. Ergo, Bolton’s eschewing of diplomatic niceties bylobbing a grenade into the proceedings weeks before the summit’s opening.

Of considerable controversy in this maelstrom of changes was Bolton’s proposal to scrap all references to the Millennium Development Goals (MDGs). Specifically, the United States asked to excise the following language: “We agree to support the establishment and implementation of country led ‘quick win’ initiatives consistent with long-term national development strategies so as to realize major immediate progress towards the development goals, including the Millennium Development Goals...” In its place, Bolton proposed the document only refer to “internationally agreed development goals.” The basis of his argument was that renaming and realigning the MDGs would avoid commitment on specific—and contentious—means of achieving the goals.

One such contentious strategy outlined and embodied by the MDGs is the 35-year commitment of developed countries to provide 0.7% of their GNP to official development assistance. The MDGs also focus on utilizing official development assistance to achieve goals, 18 targets, and 48 indicators by the year 2015; a commitment agreed to in September 2000 by all 191 UN member nations, including the United States. The eight goals and their accompanying targets include:

- **Eradicating extreme poverty and hunger.** Target 1: Halve the proportion of people whose income is less than one dollar a day; and Target 2: Halve the proportion of people who suffer from hunger.
- **Achieving universal primary education.** Target 3: Ensure that children everywhere, boys and girls alike, will be able to complete a full course of primary schooling.
- **Promoting gender equality and empowering women.** Target 4: Eliminate gender disparities in primary and secondary education, preferably by 2005, and in all levels of education no later than 2015.
- **Reducing child mortality.** Target 5: Reduce by two thirds the mortality rate for children under five years of age.
- **Improving maternal health.** Target 6: Reduce by three quarters the maternal mortality ratio.
- **Combating HIV/AIDS, malaria, and other diseases.** Target 7: Have halted and begun to reverse the spread of HIV/AIDS; and Target 8: Have halted and begun to reverse the incidence of malaria and other major diseases.
- **Ensuring environmental sustainability.** Target 9: Integrate the principles of sustainable development into country policies and programs and reverse the loss of environmental resources; Target 10: Halve the proportion of people without sustainable access to safe drinking water and sanitation; and Target 11: By 2020, achieve a significant improvement in the lives of at least 100 million slum dwellers.

How does one object to making the right to development a reality for everyone and to freeing the entire human race from want? How does one object to the idea that progress is based on sustainable economic growth, which must focus on the poor, with human rights as the centerpiece? How does one object to goals that reflect a comprehensive approach to “tackling many problems simultaneously across a broad front,” as defined in the MDGs-related declaration issued five years ago?

Thankfully, the final “Outcomes Document” adopted September 14, 2005, by the world’s leaders reflects a repudiation of the United States’ attempt to eliminate the MDGs from the global agenda. Yet, even given such a positive result, the UN’s attempts to convince world leaders that a combination of poverty, drought, famine, and HIV/AIDS threatens more human
lives than terrorism ever has, were roundly defeated. In UN Secretary-General Kofi Annan’s assessment of the document, “[it] is not all that we had hoped for.”

It is incumbent upon those whose task it is to advocate the needs of the world’s most vulnerable citizens to combat, via alliances of conscience, any attempt to reverse hard-won advances in the arena of human development. From the perspective of the International Association of Physicians in AIDS Care (IAPAC) and our global membership, it is our duty to defend the health of those men, women, and children who rely on our work not only to remain alive, but indeed to live healthy and productive lives.

The MDGs are so important to our work that IAPAC this year is recognizing their author and most vocal cheerleader, Jeffrey D. Sachs, with our 2005 Jonathan Mann Health-Human Rights Award. As Special Advisor to the UN Secretary-General on Human Development, Sachs’s message is an extension of insights advanced by the late Jonathan Mann, who himself was a pioneer in the arena of health-human rights.

Sachs understands, as Mann did, that the attainment of human rights is a matter of “progressive realization.” This principle suggests that the world community will achieve the MDGs by making steady progress toward the prize. And because, as Martin Luther King Jr. once noted, “the arc of history is long, but bends toward justice,” traveling along this arch and realizing its benefits is a progressive process, one that we hope is infused with a certain self-consciousness about coming into being.

Proposals such as those made by the US diplomatic corps in the weeks preceding the 2005 World Summit represent a symbolic interruption that has severe consequences for our march toward progress. We can only hope that the 2005 World Summit—indeed, the world community—can get us back on track to rediscovering something we almost lost.

José M. Zuniga is President/CEO of the International Association of Physicians in AIDS Care (IAPAC), and Editor-in-Chief of the IAPAC Monthly.
1. Emtricitabine (FTC), a new nucleoside reverse transcriptase inhibitor (NRTI), was approved by the US Food and Drug Administration (FDA).

2. A new protease inhibitor (PI), atazanavir (ATV), as well as fosamprenavir (FPV), a pro-drug of the PI amprenavir (APV), were approved by the FDA.

3. Enfuvirtide (ENF), the first drug in the new class of fusion inhibitors and an injectable drug, was approved by the FDA.

4. The World Health Organization (WHO) announced its “3 by 5” initiative, which is meant to assist developing nations in acquiring antiretroviral drugs, resulting in a planned 3 million people in resource-constrained countries being placed on antiretroviral therapy by December 2005.

5. In his State of the Union address, US President George W. Bush proposed spending US$15 billion over the next five years to combat AIDS in 12 African and two Caribbean countries. The program would come to be known as the President’s Emergency Plan for AIDS Relief (PEPFAR).

6. Population estimates for the year 2050 were reduced by 0.4 billion to a total of 8.9 billion, due to the potential impact of HIV/AIDS.

7. Research indicated that European programs supplying sterile needles to injection drug users had been effective, nearly eliminating HIV transmission through needle drug use in France, Germany, and the United Kingdom. Transmission had also been significantly reduced in similar programs.

8. The new Director-General of the WHO, South Korean Lee Jong-Wook, stated in his first address that HIV/AIDS would be the top priority of the organization under his tenure.

9. The South African government approved the distribution of free antiretroviral drugs in public hospitals. According to the plan, within one year antiretroviral drugs would be available through at least one service point in every South African health district; within five years, every local municipality would have one service point.

10. The United Nations (UN) World Food Programme announced that the emphasis of its humanitarian aid efforts in southern Africa would be changed from emergency food supply to the provision of assistance specific to HIV/AIDS patients, including nutritional support, awareness campaigns, and other services targeted to those infected with HIV.

References

Detectable viral loads and slow development of resistance

Chris Gadd

HIV-infected patients on antiretroviral therapy but with detectable levels of HIV in the blood are at risk for emergence of increasingly resistant virus. To gain a better understanding of the risk of developing antiretroviral drug resistance, investigators from the University of North Carolina enrolled 98 adult patients from their HIV clinic who had been on a stable antiretroviral regimen for at least six months but had detectable viral loads. All of the patients had two genotypic resistance tests, taken at least 30 days apart.

Most of the patients had substantial treatment experience, with a median of three prior regimens and six antiretroviral drugs. At the start of the study, the median CD4 count was 246 cells/mm³ and the viral load was 7,940 copies/mL, with 55% of the patients on a protease inhibitor (PI)-based drug regimen.

At the first genotypic test, 88% of the patients had at least one resistance mutation, with a median of three per patient. Resistance mutations were defined according to International AIDS Society-USA recommendations. After a median follow-up of 9.3 months, 60% of the patients had acquired at least one new mutation. CD4 counts had remained stable at a median of 242 cells/mm³ but viral loads had risen to 20,000 copies/mL. The investigators calculated that the risk of a new mutation was associated with the average viral load across the study (<0.001), the rate of change of viral load (<0.001), and the number of mutations detected at the first resistance test (<0.001). However, they found no link between the risk of new mutations and CD4 count, viral load, sex, race, age, or the number of antiretroviral drugs or regimens previously received.

Specifically, they saw that patients with average viral loads between 1,000 copies/mL and 10,000 copies/mL were twice as likely to develop new mutations than those with higher or lower average viral loads. “Occurrence of new mutations is a function of replication rate, and at HIV RNA levels less than 1,000 copies/mL, ongoing continuous rounds of replication are likely to be low,” the investigators explain. “Conversely, at higher replication rates new mutations are more likely to occur.”

Patients with viral loads rising at a rate of 0.2 log₁₀ per month were also at a 2-fold greater risk of new mutations than those with stable or falling viral loads.
This, the investigators argue, is due to high replication rates allowing any drug-resistant virus particles to increase in number more rapidly.

Finally, having no mutations at the start of the study was also an independent risk factor for the risk of mutations developing, with these patients being at more than three times the risk of developing mutations than those with one to three mutations, and around twice as likely as those with more than three mutations. This could be due to the decreased fitness of HIV with multiple mutations, leading to lower replication rates.

Limitations of this study include the inability of the genotype tests used to detect mutations present in small numbers. The tests were also unable to detect resistance mutations for the fusion inhibitor enfuvirtide (ENF), which was being taken by two (2%) of the 98 patients.

“Further studies monitoring resistance evolution over time are needed, and combined analyses across observational cohorts would strengthen our initial observations,” the investigators conclude.

Reference
The prevalence of recreational crystal methamphetamine use and related emergency room admissions are on the rise across the United States, accompanied by a curious media sometimes quick to sensationalize the trend, other times to isolate its impact on specific social groups (eg, gay and bisexual men, circuit party attendees). According to the World Health Organization (WHO), amphetamines are the second most commonly used and abused controlled substances, after cannabis. More than 35 million people regularly abuse these substances.

Even episodic or intermittent use of methamphetamines is associated with risky sexual practices likely to transmit HIV, such as unprotected anal intercourse (UAI) with serodiscordant sex partners. To the chagrin of public health scholars, crystal methamphetamine use has exploded concurrently with two other disconcerting trends: first, an increase in new HIV infections, particularly within the gay dance “circuit” and, on average, among an older cohort of gay men (eg, the average age of a newly infected gay man in New York in 2005 is around 40 years) and second, a rise in antiretroviral (ARV) drug resistance within already-infected individuals. Antiretroviral drug resistance is a primary cause of treatment failure, is connected with neurological damage, and is linked to increased mortality. It therefore behooves researchers interested in treatment efficacy and group health to inquire into the relationship between crystal methamphetamine (ab)use and ARV drug resistance.

The crystal methamphetamine use-HIV infection-ARV drug resistance nexus is troubling. This is perhaps nowhere more pronounced than for communities of men who have sex with men (MSM), which are already encumbered by the persistence of risky sexual practices, including a resurgence of UAI and other activities associated with HIV transmission. Crystal methamphetamine use is often a culprit during seroconversion. One Los Angeles study found that 61% of gay and bisexual men seeking treatment for crystal methamphetamine dependence were infected with HIV. A recent San Francisco study also found that HIV incidence among methamphetamine users was statistically higher than among non-users, with users at least three times as likely as nonusers to be HIV-positive. These studies, along with others, suggest that crystal methamphetamine use is a common co-morbidity among HIV-positive individuals, whose viral loads also increase in its presence.

Crystal methamphetamine-using seropositive individuals are at greater risk for ARV drug resistance, a relationship that is attributable to one or more of three causal mechanisms, of which two are clinical and one is behavioral.

- **Cellular suicide.** Crystal methamphetamine use stimulates the secretion of tumor necrosis factor (TNF), a cytokine whose levels are already high in HIV-positive individuals. High levels of TNF trigger a biochemical pathway that leads to cellular suicide, a condition known as apoptosis. In HIV-positive people, crystal methamphetamine boosts TNF levels, which can induce CD4 apoptosis. This facilitates increased viral replication and thus reduced ARV effectiveness.

- **Metabolism rates.** Crystal methamphetamine can alter ARV drug absorption and breakdown, expediting elimination of ARV drugs via metabolic pathways as a result of drug-drug interactions.
Accelerated metabolism of ARV drugs lowers bloodstream levels to below the threshold required to manage the virus. This can increase viral loads, prompting the onset of resistance. Indeed, this is precisely what a recent San Diego study found: crystal methamphetamine-using seropositive individuals on highly active antiretroviral therapy (HAART) experienced higher viral loads than those on therapy who either had never tried crystal methamphetamine or who had been clean for at least 30 days.

**Adherence.** There is a behavioral link between crystal methamphetamine and ARV drug resistance through methamphetamine’s association with inadequate adherence to dosing schedules. In other words, crystal methamphetamine use can impair adherence. Sporadic adherence contributes to ineffective inhibition of viral replication and thus the onset of ARV drug resistance.14

In addition to compromised HAART effectiveness, the HIV-crystal methamphetamine nexus may also produce potentially fatal effects. In the human body, CYP2D6 is a liver enzyme that metabolizes both methamphetamines and protease inhibitors (PIs). Some PIs—especially ritonavir (RTV) and delavirdine (DLV)— have a greater affinity for this enzyme than do methamphetamines. When taken together, CYP2D6 will metabolize the PI before it will metabolize crystal methamphetamine. Delayed metabolizing of crystal methamphetamine allows levels in the bloodstream to rise to dangerous levels, especially in the brain—a 3- to 10-fold increase—which can result in fatal overdose.1,17

Although research on the clinical and behavioral mechanisms of ARV drug resistance is growing, the above discussion demonstrates the need for continued investigation. This article reports the results of a pilot study that is part of a larger project exploring the correlates of ARV drug resistance.

**Methods**

**Sampling strategy.** Participants in the present study comprise a purposive sample of 38 physicians who are members of the International Association of Physicians in AIDS Care (IAPAC), a Chicago-based non-profit medical association that represents a professional membership of more than 12,000 physicians and other health care providers in more than 103 countries. Physician-members were surveyed at the IAPAC North American Sessions 2005, held June 3-4, 2005, in Chicago. This IAPAC-sponsored study is part of a larger, longitudinal study on the behavioral and clinical correlates of ARV drug resistance.

**Instrument and statistical analyses.** Physicians were asked to complete a 45-item questionnaire that contained a series of questions pertaining to their HIV-positive patients. Questions were clustered into five themes:

- physician’s practice and patient profile;
- medication, adherence, resistance;
- illicit drug use;
- psychiatric symptoms; and
- sexual activity.

Two-tailed, Pearson’s product-moment correlations were computed across items for behavioral and clinical cofactors. Because analyses were conducted on a small, purposive sample, results should be interpreted as indicating trends that signal the need for further investigation.

**Results**

**Physician practice and patient profile.** On average, 60% of IAPAC physician-members’ patients are HIV-infected; 55% are gay men. Five percent of the physicians see one to five HIV-positive patients per week; 21% see six to 10 per week; 29% see 11 to 20 per week; 24% see 21 to 50 per week; and 21% see more than 50 HIV-positive patients per week. Seventy-six percent of HIV-positive patients are on HAART. Forty-five percent of the patients are on an RTV-containing regimen, 3% on a DLV-containing regimen. At the time of the survey, 55% had undetectable viral loads, 20% were resistant to just one ARV drug, and 30% to multiple ARV drugs. Fifty-two percent of patients self-report taking an ARV “drug holiday” specifically because of illicit drug use. Only one third of the patients were described as being “very well informed” about the relationship between drugs and HIV.

Patients reported to their physicians a variety of socio-sexual behaviors. Fifteen percent of patients used Internet-based services to arrange sex, 13% had visited a bathhouse, and 8% had attended a circuit party. Twelve percent of patients self-report insertive UAI in the past six months; 8% report receptive UAI. Twenty-one percent of those who reported any type of UAI said they were using crystal methamphetamine at the time the UAI occurred. Another 32% of patients were high on another substance, and 53% of patients had consumed alcohol prior to or during the sexual encounter. Physicians believe that slightly more patients are “very well informed” about the relationship between drugs and sex (43%) than are very well informed about the relationship between such drugs and HIV (33%).

**Crystal methamphetamine and resistance: Behavioral risk factors.** Crystal methamphetamine use at one point in time increases the likelihood of future use. Crystal methamphetamine use in the past week is positively correlated with use in the past month \( r = 0.975, P < 0.001 \), use in the past three to six months \( r = 0.833, P < 0.001 \), and use in the past 12 months \( r = 0.908, P < 0.001 \). The use of crystal methamphetamine is associated with a series of risk factors connected to ARV drug resistance. For example, those who report crystal methamphetamine as their most commonly ingested drug within the past month show a trend for missing a medication dose in the past month \( r = 0.417, P < 0.085 \). Crystal methamphetamine users also participate in high-risk lifestyles.
Those who used crystal methamphetamine in the past week, month, or 12 months were more likely to have gone to a bathhouse (r = 0.387, 0.374, and 0.422, respectively; \( P < 0.05 \)) and circuit party (r = 0.667, 0.657, 0.613, respectively; \( P < 0.001 \)).

Crystal methamphetamine use is also connected to incidences of UAI. Those who used crystal methamphetamine in the past week, past month, and past 12 months were more likely to engage in insertive UAI (r = 0.662, 0.626, 0.541, \( P < 0.001 \)) and receptive UAI (r = 0.792, 0.729, 0.640, \( P < 0.001 \)), two high-probability HIV transmission-related sexual behaviors.

**Crystal methamphetamine and resistance: Clinical risk factors.** The survey instrument did not solicit specific information on TNF, metabolism, or CYP2D6. Results on the clinical aspect of the crystal methamphetamine/resistance relationship are therefore limited. Results do, however, suggest that those who used crystal methamphetamine in the past three to six months were also likely to be on an RTV-containing regimen (r = 0.335, \( P < 0.028 \)), which exacerbates the likelihood of a fatal drug-drug interaction. Those patients who self-report crystal methamphetamine as their most commonly ingested drug show a trend for being resistant to multiple ARV drugs (r = 0.446, \( P < 0.083 \)). The most substantively noteworthy finding, however, is that crystal methamphetamine use in the past week, month, three to six months, or 12 months is not correlated with having an undetectable viral load (r = 0.014, \( P < 0.939 \); r = 0.071, \( P < 0.697 \); r = 0.001, \( P < 0.995 \); and r = -0.028, \( P < 0.879 \), respectively). If the counterfactual is true, then those who do not report crystal methamphetamine use are likely to be those for whom HAART is effective and vice versa.

**Discussion**

It should be noted that results stem from a pilot study of 38 physicians attending the IAPAC North American Sessions 2005. Results are not intended to be definitive and generalizable without qualification, but rather suggestive of the viability of a potential behavioral and clinical relationship between crystal methamphetamine use and ARV drug resistance. The intent is to document trends and relationships to motivate further inquiry.

Results reveal that clinical and behavioral pathways undergird the relationship between crystal methamphetamine use and ARV drug resistance. The still-nascent literature emphasizes the role of inadequate adherence as a critical behavioral factor responsible for resistance. Study results are confirmatory. The possibilities for addiction are in place as patients who report using crystal methamphetamine at one point in time are also likely to report future use. Addiction concerns aside, crystal methamphetamine users are more likely to engage in a number of HIV-transmittable sexual behaviors such as insertive and receptive UAI. These findings are especially troubling in light of the fact that crystal methamphetamine users are more likely to visit bathhouses and attend circuit parties, where there may be an overall high prevalence of seropositive patrons and riskier sexual practices.

The public health threat is exacerbated given that: (1) seropositive individuals exhibit a less cautious sexual profile, (2) crystal methamphetamine-using seropositive individuals are less likely to be adherent to their ARV regimen (which then increases the likelihood of ARV drug resistance), and (3) crystal methamphetamine-using seropositive individuals on HAART are likely to have higher viral loads.

Study results corroborate the role played by behavioral and clinical factors in the relationship between crystal methamphetamine and ARV drug resistance. Although instrument limitations precluded testing for the direct or indirect role played by ARV drug metabolism, neurological damage, or apoptosis, results did reveal that those individuals who reported using crystal methamphetamine in a variety of different time periods were not likely to have undetectable viral loads. If the reverse is also true (ie, that those who do not use crystal methamphetamine are statistically more likely to have undetectable viral loads), then there is further evidence for a clinical relationship between crystal methamphetamine use and ARV drug resistance. Much more research is required into this important and growing area of public health concern.

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**References**


24. The data indicate that crystal users are likely to attend bathhouses and circuit parties. The survey instrument did not, however, inquire into the sexual practices (safer versus less safe) at these respective venues.


Night falls with a thud in the tropics. Yet the sun rises with circumspection.

Nontropical travelers to the 3rd IAS Conference on HIV Pathogenesis and Treatment, held July 24-27, 2005, in Rio de Janeiro, learned this when one minute they sat, backs to breakers, breasting the sun’s setting rays—and the next minute they groped hotelward in spryly dying light. Rio de Janeiro lies just degrees north of the Tropic of Capricorn, but far enough to ensure tropical climes in July (the dead of winter) and this scuttling afternoon sun.

What explains this wry inversion of expectations for those rooted to Earth’s more boreal reaches? AIDS conference crawlers, if not scientists, at least aver a scientific bent and should know stuff like this. We vaguely grasp that the tropical sun’s less wayward year-round arc has something to do with it. But what exactly?

Then there are those preposterous downtown peaks—Sugar Loaf et al—that wrench gasps of admiration even from tourists well prepared for these iconic monoliths. Sheer promontories in center city—decidedly nonvolcanic islands stuck squarely inland—invert long-held notions of geographical propriety. We may cablecar to their summits and watch the sun tumble with yet greater drama.
But who among the science-minded can construe their ancestry? 2

Rio, even the blinkered attendee soon saw, abounds in ripe inversions of ready presumption. Unlike most cities where the wealthy build on hills to reap clean air and views, in Rio the poor command the aerie prospects too treacherous for massy mansions. And anyone expecting a river in Rio had best consult the plucky Portuguese navigators keen enough to chart a winter Atlantic crossing but— arriving on January 1, 1502—incurious enough to see if a mouthing river really explains Rio’s roomy Guanabara Bay. 3

Another geophysical inversion: About an hour after boarding buses for the conference center, attendees learned that the site, “Rio Centro,” is not in central Rio. Or even the near suburbs, apparently. But this disappointed propinquity had its merits: all the more time to canvass abstracts, map the day’s itinerary, or mull a career jump to Brazilian traffic planning.

And in perusing those abstracts one soon deduced a happier inversion: A copious load of conference reports came from tropical and subtropical lands with lush HIV epidemics. That means much more at this biennial IAS conclave, because the conference focuses solely on basic and clinical research, leaving socioeconomic worries to the interleaved International AIDS Conferences.

Of the 803 reports at the 1st IAS
Conference on HIV Pathogenesis and Treatment, held in Buenos Aires in 2001, 193 came from countries other than the United States, Canada, Australia, Japan, Israel, and those in western Europe. Rio outdid that 1-in-4 ratio with 565 reports from poor or middle-income countries versus 1,421 from western Europe and allied plutocracies—a 2-in-5 ratio.

Then there were those most important inversions—the dashed or endorsed expectations that reverse or confirm hopes of bringing HIV to heel. Rio offered rich examples, which this article hopes of bringing HIV to heel. Rio that mutilating female circumcision likely. But researchers bent on proving incidence in men, the first randomized
circumcision found that it does indeed cut the risk of HIV infection, but
• Scarifying “female circumcision,” to
the consternation of all, appeared to protect women from viral intruders.
• While several studies underlined the threat of transmitting drug-resistant HIV,
• A big pediatric trial failed to confirm that resistance testing helps pick a better new regimen.
• As researchers from South America and southern Africa confirmed the durability of antiretrovirals (including generics) there,
• Workers in Uganda tried (unconvincingly) to certify the merits of first-line triple nucleoside reverse transcriptase inhibitors (NRTIs).
• And while evidence of frequent cross-clade HIV superinfection emerged in the literature,
• One team found hints of a feeble HIV.

EPIDEMIC LESSONS

Everyone knows certain measures ward off HIV. Or do they? With mountains of cohort data nominating circumcision as a likely expedient for lowering HIV incidence in men, the first randomized trial of foreskin trimming found that—yes, indeed—it makes HIV infection less likely. But researchers bent on proving that mutilating female circumcision
heightens HIV risk in women could not explain away numbers that argued the opposite.

Work from California showed that human papillomavirus (HPV) infection bolsters the odds of HIV infection via anal sex between gay men, while research on the other side of the continent confirmed high risks of transmitted drug-resistant virus. Countering steady trends in adult studies, a large European pediatric trial found that resistance testing did not help pick better rescue regimens for kids.

Is circumcision the kindest cut?

Maybe this conference’s most important report came in a slide session on sexual transmission of HIV, when Bertran Auvert (University of Versailles Saint-Quentin, France) unveiled the first randomized trial evidence that circumcision limits HIV risk in heterosexual men [abstract Tu0402]. That conclusion seemed a cinch since one cohort study after another buttressed commonsensical notions that foreskin snipping may stymie HIV in several ways:
• Lowering risk of ulcerative sexually transmitted diseases that pave avenues for HIV
• Negating occasions for foreskin micro-trauma, another HIV portal
• Getting rid of foreskin Langerhans cells, primary HIV targets
• Making other genital lesions more obvious—and hence more treatable

But all the good reasons in the world don’t add up to proof. Only randomized controlled trials crank out evidence physicians can confidently take to the clinic. Auvert’s trial is not the only randomized effort to test circumcision’s value. But it is the first to yield results.

Auvert recruited 3,128 healthy men without HIV infection in Orange Farm, an urban enclave near Johannesburg, South Africa. There are no oranges, Auvert averred, and there is no farm. But there’s lots of HIV infection: Adult prevalence stands at 32%. These 18- to 24-year-olds were randomly assigned to undergo circumcision by a physician or to remain uncircumcised. Everyone agreed to follow-up visits three, 12, and 21 months after randomization, when workers tested them for HIV and drummed in safe sex lessons.

All enrollees could opt for foreskin fleecing after 21 months, but follow-up didn’t last that long for most. Preliminary results convinced trial watchdogs to stop the study early when HIV incidence in the control group rose disproportionately fast. After 4,664 person-years of follow-up, Auvert counted 51 infections among uncircumcised men and 18 in the circumcised group. That put incidence at 2.2 HIV infections per 100 person-years in the control group versus 0.77 with circumcision.

In an analysis not adjusted for confounding variables, the circumcised men had a 65% lower risk of HIV infection. Adjusted analyses showed similar rates of protection in the intervention group (Table 1). Auvert figured that foreskin removal spared six or seven of 10 men from HIV infection.

As cheering as these results are, the duly circumspect agree that results of ongoing randomized trials in Kenya and Uganda must confirm Auvert’s findings before anyone proclaims success. Auvert himself stressed that circumcision falls far short of 100% protection. Failure to grasp that plain fact could drive HIV incidence up if freshly pruned young men start having lots more rubber-free sex. And having sex with circumcised men does nothing to protect a woman. Finally, Auvert’s study says nothing about transmission risk between gay men.

Just as surely as foreskin clipping seems a safe bet to cut HIV transmission in men, so the various bloody ablations labeled female circumcision seem certain to lift transmission risk in women. The tainted lancets often used in these rough-and-ready surgeries may carry HIV from one woman to the next; the resulting genital
5,753 women (84%) who agreed to anonymous HIV testing. Stallings used that group to probe for bivariate links between HIV risk factors and both circumcision and HIV serostatus. Then, to adjust circumcision status for factors proving significant in bivariate analyses, she built logistic regression models in a subgroup of 5,284 women who ever had intercourse.

None of the variables Stallings weighed explained why circumcision apparently protected women from HIV in the primary analysis—and she weighed a lot of them: region, years living there, household wealth, age, education, religion, years sexually active, union status, polygamy, number of recent and lifetime sex partners, recent infection or abnormal discharge, use of alcohol, and ability to say no to sex.

In the final model, circumcision whittled the risk of HIV infection by 40% (odds ratio [OR] 0.60, 95% confidence interval [CI] 0.41 to 0.88). That model also yielded the unsurprising finding that genital ulcer disease for 12 months or more raised the HIV risk 2.20 times (95% CI 1.28 to 3.77). Stallings’ study also confirmed that male circumcision has no impact on HIV risk factors and both circumcision and HIV risk 2.20 times (95% CI 1.28 to 3.77). Stallings’ study also confirmed that male circumcision has no impact on women’s HIV risk. She closed with the slender hope that “anthropological insights on female circumcision as practiced in Tanzania may shed light on this conundrum.”

### Table 1. Risk of HIV with or without circumcision in a randomized trial

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Rate ratio (95% CI)</th>
<th>Protection rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.35 (0.20 to 0.60)</td>
<td>65% (40% to 80%)</td>
</tr>
<tr>
<td>Adjusted for age, religion, ethnic group, alcohol consumption, recruitment period</td>
<td>0.33 (0.19 to 0.57)</td>
<td>67% (43% to 81%)</td>
</tr>
<tr>
<td>Adjusted for mental status, condom use, number of sex partners or contacts</td>
<td>0.34 (0.20 to 0.59)</td>
<td>66% (41% to 81%)</td>
</tr>
<tr>
<td>Per protocol*</td>
<td>0.25 (0.14 to 0.46)</td>
<td>75% (64% to 86%)</td>
</tr>
</tbody>
</table>

*Eliminates men randomized to circumcision who did not have the procedure and vice versa. CI = confidence interval. Source: Bertran Auvert, abstract TuOa0402.

### Epidemic heads for a second generation

For some years, epidemiologists have warned that the first generation of infants infected at birth with HIV would soon be old enough to have sex, have children, and transmit the virus on to them. That day arrived a few years ago, reported Michelle McConnell from the US Centers for Disease Control and Prevention (CDC) with colleagues in New Jersey, Puerto Rico, Texas, and US National Institutes of Health (NIH) clinical trials sites [abstract MoPcLB9.5C01].

Gathering facts from chart reviews and interviews from March 2002 to June 2004, the CDC team found 18 pregnant or previously pregnant youngsters infected by their mothers. The group included eight Hispanics and five African Americans with a median age of 18 years (range 15 to 25 years) at the time of the interview. Only five of them (28%) were raised by at least one of their parents. Among the eight young women who bore a child most recently, all eight did so by cesarean section. Their median CD4 count during pregnancy measured 304 cells/mm³, and they had median viral loads of 7,238 copies/mL when they started prenatal care and 1,554 copies/mL at delivery. All eight were taking antiretrovirals during pregnancy, but only seven did at labor and delivery.

Fifteen of these 18 young women (83%) did not intend to become pregnant. Their median age when they did was 17 years (range 13 to 20 years), and their median age when they first had sex was 15 years (range 10 to 19 years). Of the 23 pregnancies recorded, three are ongoing, one resulted in miscarriage, and nine ended with elective abortion. One of the 10 babies born came into the world with HIV.

Among the 11 women who most recently gave birth or are still pregnant, seven began prenatal care during the first trimester and eight had genotypes for resistance mutations. Genotyping may help clinicians make sure these pregnant youngsters do not pass resistant virus to their infants. But genotyping did not help pick better regimens in a randomized trial of 170 children with a detectable viral load and at least two years of experience with at least two NRTIs [abstract WeOa0106]. Carlo Giaquinto (University of Padova, Italy) and colleagues sniffed out several factors that may explain this surprising result.

Clinicians in Italy, Brazil, the United Kingdom, Spain, Germany, and Portugal randomized 87 children to start a new regimen based on resistance testing and 83 to try a new combination picked without genotyping help. Several adult trials of resistance testing offered clinicians expert advice in interpreting genotypes, and at least two adult studies show that sage counsel pays off.5,6 Although clinicians in Giaquinto’s PERA trial could tap steering committee virologists for help, they did not receive expert advice “as a matter of course.”

After 48 weeks of rescue therapy, viral load drops averaged 1.23 log copies/mL in the genotyping group and...
1.51 log copies/mL in the control group, a nonsignificant gap. This tiny difference dwindled even more by 96 weeks. Nor did the groups differ much in proportions with a viral load below 50 copies/mL at 48 weeks (19% genotyping, 21% control) or 96 weeks (21% genotyping, 18% control). The genotyped group did enjoy a slightly better (2.5%) CD4-cell gain after 96 weeks (P = 0.06).

Why did genotyping flop as a rescue planner in PERA? Giaquinto suggested several reasons in introducing his study—greater difficulty in suppressing viremia among children than adults, more adherence problems with kids, and fewer antiretroviral options for children. But he also uncovered more specific reasons for genotyping’s undoing.

First, substantially more children in the genotyping group (56%) than the control arm (19%) were prescribed didanosine (ddI) and stavudine (d4T) as their NRTI backbone. Why? The VirtualPhenotype assay used consistently signaled viral sensitivity to these NRTIs in the genotyping group, though Giaquinto aptly observed “these drugs are less likely to be sensitive with more prior exposure and this may explain the effect on virological response.”

Second, while 49% of genotyped children continued one or more NRTIs from their starting regimen, only 19% in the control group did so (P < 0.01). On the other hand, significantly more control arm children (55%) than genotyped children (43%) recycled one or more drugs from a previous regimen (P < 0.01). The most-continued drugs in the genotyping group were ddI and d4T, while control group physicians usually recycled zidovudine (AZT) and lamivudine (3TC). Numerous studies demonstrate the value of mixing AZT and 3TC and the toxic risk of combining ddI and d4T.

Third, Giaquinto turned up one ironic chit of evidence suggesting that genotyping-arm clinicians would have fared better without test results. Before randomization researchers asked all physicians, “If this child is randomized to no resistance testing, what regimen would you prescribe today?” An overwhelming 82% in of the genotyping docs named at least one drug in this hypothetical regimen that differed from the ones they gave after seeing genotypic results. But only 18% in the control group switched a drug when they actually got around to prescribing (P < 0.001).

If one assumes steering committee virologists would have steered physicians away from ddI and d4T—understanding the unreliability of phenotypic readings at the time of this 2000-2003 trial—routine expert advice may have turned the result in genotyping’s favor.

On the prowl with patient zero
In his frisson-filled look at the US epidemic’s first days, And the Band Played On, Randy Shilts assigned the tag “Patient Zero” to the Canadian flight attendant who purportedly brought HIV to North America and kept spreading it with abandon. Randy Shilts assigned the tag “Patient Zero” to the Canadian flight attendant who purportedly brought HIV to North America and kept spreading it with abandon. Whether Blick is right about his Patient Zero matters less than how many Patient Zeros are on the street swapping viruses with known and anonymous paramours. Blick himself counted three—the New York City man (who kept having sex until he got sick), the Connecticut man, and the Connecticut man’s “open-relationship” partner of 12 years, who shares a similar multimutant virus. This partner also ended up on the giving end of anal sex with the New York man last October but claims he didn’t ejaculate.

Blick was clued to his patient’s potential donor role by QUEST Diagnostics, which spotted a 99.5% pol gene match between his virus and the New York man’s strain. At the XIV International HIV Drug Resistance Workshop, held June 7-11, 2005, in Québec City, Canada, Ron Kagan from QUEST reported uncovering 12 sequences from four people (one the Connecticut man) that nearly mirrored the mutations in the New York case—four out of 153,000 studied. An interesting and little-mentioned demographic in the New York case is the man’s age. He had reached his late 40s by the time he took home his furious virions. The Connecticut man is even older—52 according to Blick’s records—and his steady party companion is 41. These are no wild youths fresh from the provinces and keen to score big in the Big Apple.
They’re old enough to know something about HIV. And the Connecticut men have taken antiretrovirals for nearly a decade. The New York man and the alleged Patient Zero share another trait—fondness for methamphetamine. As reported at the Resistance Workshop10 and again in Rio for methamphetamine. As reported at the Patient Zero share another trait—fondness taken antiretrovirals for nearly a decade. And the Connecticut men have They’re old enough to know something about HIV. And the Connecticut men have

Took.11 And a clinic-based risk of having unprotected sex as people with high-risk of HIV transmission run nearly twice the ART or having a low viral load prevents HIV transmission. A meta-analysis by CDC math majors found that HIV-infected people who think taking antiretroviral therapy (ART) or having a low viral load prevents HIV transmission run nearly twice the risk of having unprotected sex as people without those beliefs.11 And a clinic-based Connecticut study figured that only 5% of people practicing high-risk sex had resistant virus, but that core group accounted for a high proportion of dangerous liaisons.12

At least in this North Carolina cohort, four of five infected people still not taking antiretrovirals apparently assume immunity to reinfection with another (possibly resistant) virus, while people taking antiretrovirals are more cautious. Those findings run counter to the meta-analysis finding that people taking antiretrovirals apparently assume immunity to reinfection with another (possibly resistant) virus, while people taking antiretrovirals are more cautious. Those findings run counter to the meta-

Table 2. Independent predictors of HIV in 1,409 gay men

<table>
<thead>
<tr>
<th>Relative hazard</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three or more anal HPV types</td>
<td>3.3</td>
<td>1.1 to 9.9</td>
</tr>
<tr>
<td>Unprotected anal sex*</td>
<td>7.2</td>
<td>2.6 to 20.0</td>
</tr>
<tr>
<td>Methamphetamine use†</td>
<td>6.8</td>
<td>2.6 to 18.0</td>
</tr>
<tr>
<td>Atypical squamous cells</td>
<td>2.8</td>
<td>1.1 to 7.9</td>
</tr>
</tbody>
</table>

*With partner with unknown HIV status in previous six months.
†In previous six months.
Source: Peter Chin-Hong, abstract TuOa0403.

Sonia Napravnik (University of North Carolina at Chapel Hill) extended this research in a study of 303 HIV-infected people that linked both bad adherence and resistant virus to jeopardous sex [abstract MoPp0203]. The study group included 201 men and 102 women, 73 whites and 230 nonwhites, and 22 who abused alcohol. None of those variables swayed the risk of unprotected sex, defined as condom-free sex with one or more partners in the past year. Several other variables did favor unsheathed dalliance:

- Age under 45 years (45% having unprotected sex) versus 45 or older (28%) (P < 0.01)
- Men who have sex with men (MSM) (48%) versus others (36%) (P = 0.06)
- Illicit drug use (48%) versus no illicit drug use (37%) (P = 0.08)
- ART-naive (80%) versus on ART (35%) and off ART (47%) (P = 0.07)
- ART for two or more years (48%) versus fewer than two years (26%) (P = 0.05)

Napravnik had genotypes on 114 people, 45 of whom (39%) preferred coitus sans condom. Of those 45, 40 (89%) had one or more resistance mutations. The median mutation tally
in this group was 4 (IQR 2 to 6), 69% had mutations that knocked out two or more antiretroviral classes, and 27% had triple-class resistance.

Defining “inferior adherence” as missing one or more doses in the past three days, the Chapel Hill team confirmed that trait in 28% of their cohort. Among those iffy pill takers, 66% had unprotected sex versus 46% with perfect adherence. That difference made perilous sex 2.27 times more likely among wobbly adherers (95% CI 1.15 to 4.47) ($P = 0.02$).

**Peregrinations with mutations**

Airplanes have proved remarkably reliable vectors for all manner of epidemic-breeding germs. Whether Randy Shilts was right or not about a flight attendant winging the retrovirus into North America, HIV’s nearly simultaneous debarking in New York, Los Angeles, and San Francisco suggests it came by plane and not tramp steamer. Transborder SARS eruptions two years ago show that pathogens without passports still hop jets with indign impunity. And globe-trotting gays packing HIV as carry-on still pose threats to overseas pickups and regulars back home.

That conclusion came from a small but instructive survey of 64 newly diagnosed gay men from San Francisco [abstract MoPe10.7P13]. With interviews, genotypes, and detuned antibody assays, Hong-Ha Truong (University of California, San Francisco) told a story of high mobility with mutant virus by these recently infected men. The group included 49 (77%) born in the United States and 15 (23%) born elsewhere, two thirds of them white, almost all under 40 years old, and all infected with HIV-1 subtype B.

Defining HIV exposure period as the span between the last negative and first positive HIV test, Truong found that 35 men (55%) lived or traveled outside the United States during this fateful interlude. Thirty-eight (59%) had foreign-born sex partners. Among eight (12.5%) carrying major resistance mutations, seven traveled outside the United States during their exposure period and four had sex with foreign-born partners during that time. Six of these eight had NRTI-inspired mutations, three had NNRTI mutations, and two had protease inhibitor (PI) mutations.

Truong suggested that “HIV prevention strategies should incorporate specific counseling on risk of cross-border acquisition and transmission of drug-resistant HIV infection, particularly in an era of expanding antiretroviral treatment worldwide.”

**SCALE-UP STORIES**

Rio offered an ample array of studies confirming that antiretrovirals don’t stop working at the Tropic of Cancer, even though health-care setups in southern climes vary widely. In countries such as Brazil and South Africa, two conference reports showed, response rates have proved exemplary. Rio also confirmed good responses to reasonable regimens in less-heard-from regions. But so-so ART stews up North leave the same lukewarm taste down South.

**Brazilian generics working well**

Brazil’s universal antiretroviral program rests one foot on drug-company deals while planting the other on home-made generics. That stance looks solid—even more so since 2000—according to a retrospective review of Brazilians starting...
their first antiretrovirals from 1996 through 2004 [abstract MoOa0204]. At the end of 2004, reported Mauro Schechter (Federal University of Rio de Janeiro), 140,000 Brazilians were taking antiretrovirals.

Schechter’s virologic response analysis involved 485 adults (36% women) who took potent ART for at least six months and had baseline and six-month viral load readouts. Study participants came from two public health clinics, one clinical trials unit, and one private practice. Their ages averaged 38 years (±11 standard deviations [SD]) and they began their antiretroviral pilgrimage with a median viral load of 82,500 copies/mL and a median CD4 count of 185 cells/mm3 (±129 SD). More started with an NNRTI regimen (53%) than with a PI (44%), three NRTIs (2%) or a PI/NNRTI combo (2%).

As in other countries with clinical trial units, people enrolled in trials averted early virologic failure—a viral load at or above 400 copies/mL after six to nine months—more often than people in public clinics (Table 3). But Brazilians cared for in private practice did best of all, even though all three groups started with similar CD4 sums.

The substantially higher baseline load in the private clinic apparently did not dent responses in that group. That seems a little odd, since (predictably) higher pretreatment viremia correlated with higher failure risk (5.02 versus 4.50 log copies/mL, \( P < 0.01 \)), as did lower baseline CD4 counts (114 versus 193 cells/mm3, \( P < 0.01 \)). A univariate analysis teased out only two predictors of failure—starting ART before the new millennium (OR 2.71, 95% CI 1.75 to 4.2) and starting with a PI instead of an NNRTI (OR 1.48, 95% CI 1.2 to 1.8). The much higher PI use rate in the public clinic probably contributed to worse results in that group, since many may have started an outmoded unboosted PI.

How durable is ART in South Africa?

Six-month response, as in the just-reviewed study, can give a good feel for what lies down the road. But there’s nothing like hard outcomes to gauge how smoothly an ART rollout is really rolling. Linda-Gail Bekker (Desmond Tutu HIV Center, Cape Town) opened a 24-month window on response in the Usapho Lwethu (Swahili for “Our Family Clinic”) project (Figure 1), launched in September 2002 in a Cape Town district with a grim HIV prevalence of 29% [abstract MoPp0302].

Enrollees must complete six treatment training courses over three weeks and host a counselor home visit before starting therapy. Then a clinic team decides if an applicant seems ready for antiretrovirals. Usapho Lwethu uses the World Health Organization (WHO) CD4 count start signal—200 cells/mm3—or lower. Follow-up visits come four, eight, and 16 weeks after ART begins, then every 16 weeks. Counselors continue to pay two home visits monthly.

It works. So far Bekker and colleagues have screened 1,277 people and started treating 940 adults and 50 children. The group’s age averaged 34 years and 76% are girls or women. Baseline CD4 count stood at 93 cells/mm3 and viral load at 100,000 copies/mL. Nine in 10 people beginning treatment had WHO Stage 3 or 4 HIV disease. Everyone started d4T/3TC plus nevirapine (NVP) or EFV.

Through 24 months of follow-up more than 90% saw their viral load drop under 400 copies/mL and stay there (Table 4). Most of these people had a viral load below 50 copies/mL. Adherence measured by pill count stood at or above 90% through 32 months of follow-up. After one year of treatment, 7.3% had died and only 3.3% stopped returning for visits. Only 0.9% needed a second-line regimen so far.

Universal access lifts Chile

Sitting astride the Andes on the verge of Brazil’s vasty plain, Chile recently adopted its neighbor’s universal antiretroviral access rule. And the strategy seems to be working there too, reported Carlos Beltrán and Marcelo Wolff (Chilean AIDS Study Group, Santiago) [abstracts MoOa0201 and MoPe11.6C21]. By the time the Chilean team arrived in Rio, about 6,000 people had HIV on the run thanks to ART.

Beltrán and Wolff detailed responses in 2,103 people, 85% men, starting their first antiretrovirals. The median age group had lived 35 to 39 years, and

### Table 3. Virologic failure rates in Brazilians starting ART

<table>
<thead>
<tr>
<th></th>
<th>Public clinics</th>
<th>Private clinic</th>
<th>Clinical trials unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>354</td>
<td>76</td>
<td>55</td>
</tr>
<tr>
<td>Baseline CD4 count</td>
<td>179</td>
<td>206</td>
<td>199</td>
</tr>
<tr>
<td>Baseline viral load</td>
<td>71,000</td>
<td>129,000</td>
<td>75,000</td>
</tr>
<tr>
<td>Starting with PI (%)</td>
<td>52</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>Failure by month six to nine (%)</td>
<td>104 (29)</td>
<td>3 (6)</td>
<td>12 (15)</td>
</tr>
</tbody>
</table>

Source: Mauro Schechter, abstract MoOa0204

*Failure defined as a viral load at or above 400 copies/mL.

### Table 4. RNA and CD4 in South Africans starting ART

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>CD4 count (cells/mm³)</th>
<th>&lt;400 copies/mL (%)</th>
<th>&lt;50 copies/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>485</td>
<td>93</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Month 4</td>
<td>457</td>
<td>210</td>
<td>94.8</td>
<td>81.4</td>
</tr>
<tr>
<td>Month 8</td>
<td>347</td>
<td>225</td>
<td>92.5</td>
<td>80.4</td>
</tr>
<tr>
<td>Month 12</td>
<td>232</td>
<td>261</td>
<td>94.0</td>
<td>82.0</td>
</tr>
<tr>
<td>Month 24</td>
<td>91</td>
<td>383</td>
<td>96.7</td>
<td>85.7</td>
</tr>
</tbody>
</table>

Source: Linda-Gail Bekker, abstract MoPp0302.
47% had AIDS. A sizable majority, 84%, began with an AZT/3TC backbone, 44% with EFV, 29% with NVP, and 18% with indinavir (IDV).

After a median follow-up of 784 days, 143 people (6.8%) had died and 179 (8.5%) quit therapy. Beginning ART with a CD4 count under 100 cells/mm³ raised the risk of death 4.5 times. Among 1,781 people still taking antiretrovirals, three quarters continue their starting regimen.

At six, 12, and 24 months of treatment, 74%, 80%, and 80% respectively had a viral load below 400 copies/mL, while 66%, 72%, and 74% had fewer than 80 copies/mL. Virologic response did not differ by age, gender, or starting CD4 count. People with lower baseline loads responded faster, but this difference evaporated after 18 to 24 months of follow-up.

Boostered PI or triple NRTIs in Africa?

Countries new to ART mirror countries with decades-long ART histories not only in response rates, but also in which regimens work better. European and US guideline writers consistently advise against first-line triple NRTIs because even the best of such regimens come against first-line triple NRTIs because guideline writers consistently advise regimens work better. European and US Combivir) plus tenofovir (TDF) as their first antiretroviral regimen. Pontiano Kaleebu (MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda) spelled out 48-week results on 300 people in a retrospective virology substudy, including 100 from each of two Ugandan sites and 100 from the Zimbabwe cachement [abstract WeOaLB0203]. No one in DART gets real-time viral load measures.

Two thirds of the 300 substudy participants were women. Median baseline numbers were 100 cells/mm³, 279,901 copies/mL, and 37.3 years of age (range 20 to 62 years). After 48 weeks of follow-up, 38 people (13%) had stopped ART for three or more days, 17 (6%) traded AZT for d4T, and 231 (77%) continued their original regimen. Kaleebu did not account for the remaining 14.

At week 48, a missing-data-equal-failure analysis figured 65% with a viral load under 400 copies/mL and only 55% under 50 copies/mL. Respective on-treatment analysis rates were 74% and 62%. These mediocre responses match those in the AIDS Clinical Trials Group (ACTG) study comparing AZT/3TC/abacavir (ABC) (as Trizivir) with two EFV-based regimens and lag those seen, for example, with lopinavir (LPV)/RTV. After 48 weeks, 16% in DART had a viral load topping 10,000 copies/mL. These results appear to confirm the risk of starting with three NRTIs in people with a high viral load.

At week 24, the people in the CESAC program have refrigerators.

After 48 months of RTV-buoyed therapy, 28 of 30 people had a viral load under 400 copies/mL and 25 had fewer than 50 copies/mL. One of the two people who had an RNA reading above 400 copies/mL dropped below that mark after stopping antacids. The second person had a rebound after stopping all antiretrovirals during a bout of malaria. Her viral load fell below 400 copies/mL when she resumed treatment. One person couldn’t stomach RTV and returned to thrice-daily IDV with no loss of viral control.

Switching from unboosted to boosted IDV hoisted the IDV trough from 150 ng/mL to 425 ng/mL. After switching to IDV/RTV, 62% kept their RTV refrigerated while 21% relied on a thermos and 17% on traditional jars. Cissé figured that about half the people in the CESAC program have refrigerators.

Who follows WHO guidelines?

All 36 poor or developing countries responding to a WHO questionnaire about

<table>
<thead>
<tr>
<th>Table 5. Response to IDV/RTV with or without a fridge</th>
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<tbody>
<tr>
<td>Viral load &lt;400 copies/mL</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Week 4</td>
</tr>
<tr>
<td>Week 24</td>
</tr>
<tr>
<td>Week 48</td>
</tr>
<tr>
<td>IDV trough &gt;150 ng/mL</td>
</tr>
<tr>
<td>Week 4</td>
</tr>
<tr>
<td>Week 24</td>
</tr>
<tr>
<td>Week 48</td>
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</tbody>
</table>

Source: Mamadou Cissé, abstract M0pe11.7C08.
Although all respondents had clear opinions on most antiretroviral questions, only three (8%) had formal guidelines and none had published guidelines.

**FIRST-LINE TRENDS**

Probably the biggest antiretroviral news from Rio headlined TDF plus emtricitabine (FTC) as a better first-line option than tried, true, but maybe tired AZT/3TC. The conference also offered a raft of other reports on thymidine versus nonthymidine analogs, more data on intensifying therapy, three looks at a single solo-PI maintenance study, and a growth industry of research on growth hormone.

**Changing backbones**

New bone cells replace old ones all the time, but by and large we’re pretty much stuck with the same bones we’re born with. And as time wears on, those bones wear out. The spine that keeps us bipedal does a much better job in our 20s than our 80s.

Not so with NRTI backbones. These regimen ridgepoles just keep getting better. AZT/ddI, the coelacanth of nuke backbones, turned out to swim more smoothly than an evolutionary array of descendants, such as AZT/zalcitabine (ddC) and ddI/ddT. But AZT/3TC emerged as the standard spinal model, especially when fused in a single twice-daily pill.

Rio’s richest antiretroviral news came in a report showing the sterner mettle of this century’s new leading backbone contender, TDF/FTC, now bonded in a single once-daily pill (Truvada) [abstract WeOa0202]. Anton Pozniak (Chelsea and Westminster Hospital, London) spoke for a multicenter team that pitted TDF/FTC (taken once daily as separate pills) against AZT/3TC (taken twice daily as Combivir) in 509 people also starting EFV in their first antiretroviral regimen. A 48-week analysis of this ongoing 144-week trial found TDF/FTC significantly superior on virologic, immunologic, and most toxicologic grounds.

The well-matched study groups both had median viral loads around 100,000 copies/mL and 41% with CD4 counts under 200 cells/mm³. Using the US Food and Drug Administration’s pet benchmark—time to loss of virologic failure from under 400 copies/mL—Pozniak figured an 81% intent-to-treat response rate with TDF/FTC versus 70% with AZT/3TC (P = 0.005) after 48 weeks. TDF/FTC also beat AZT/3TC in an intent-to-treat sub-50-copy contest, 77% to 68% (P = 0.034). Although statisticians framed the study to prove TDF/FTC’s “noninferiority” to AZT/3TC, Pozniak noted, the CIs around these differences apparently certify TDF/FTC’s superiority.

Among people with confirmed rebounds above 400 copies/mL, genotypers saw more mutant virus in the AZT/3TC group:

- Efavirenz-related mutations: Nine (4%) on TDF/FTC versus 16 (7%) on AZT/3TC
- M184V/I: Two (1%) on TDF/FTC versus seven (3%) on AZT/3TC
- Any thymidine analog mutation (TAM): Zero on TDF/FTC versus one (<1%) on AZT/3TC
- K65R: Zero in both arms

People taking TDF/FTC gained an average 190 cells/mm³ compared with 158 cells/mm³ in the AZT/3TC group, a statistically significant (P = 0.002) though perhaps not clinically cogent difference.

Tenofovir/FTC proved significantly more tolerable than AZT/3TC. While 4% stopped TDF/FTC because of side effects, 9% shelved AZT/3TC (P = 0.016). Ten people (4%) taking TDF/FTC complained of some side effect, compared with 23 (9%) on AZT/3TC. Anemia proved the biggest problem with AZT/3TC, affecting 14 people (6%) in the AZT/3TC group and no one taking TDF/FTC.

In the kidney department, no one taking TDF/FTC saw their serum creatinine climb through week 48. While glomerular filtration slowed nonsignificantly by 1.3 mL/min with TDF/FTC, it rose 6.2 mL/min (P < 0.001) with AZT/3TC.

Lipid and fat trends appeared to favor TDF/FTC through 48 weeks of treatment:

- K65R: Zero in both arms

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Lipid and fat trends appeared to favor TDF/FTC through 48 weeks of treatment:
Thymidines versus nonthymidines

The just-reviewed NRTI results are the latest volley in a research fusillade aimed at answering one question: Should first-line NRTI backbones include or exclude a thymidine nucleoside analog? These days, that question usually means should the backbone include or exclude AZT, since no one with a choice excludes TDF. But neither thymidine nor nonthymidine analogs is a surething. Dogged resistance paladins have ineluctable short- and long-term side effects. Dogged resistance paladins also showed that some mutants evoked more toxic damage than AZT, both drugs less susceptible to nonthymidine analogs as well. And though d4T does more toxic damage than AZT, both drugs have ineluctable short- and long-term side effects. Dogged resistance paladins also showed that some mutants evoked more toxic damage than AZT, both drugs less susceptible to nonthymidine analogs as well. And though d4T does more toxic damage than AZT, both drugs have ineluctable short- and long-term side effects.

Avoiding thymidine analogs in treatment-naive people gained currency a few years back when resistance experts learned that TAMs made HIV less susceptible to nonthymidine analogs as well. And though d4T does more toxic damage than AZT, both drugs have ineluctable short- and long-term side effects. Dogged resistance paladins also showed that some mutants evoked more toxic damage than AZT, both drugs less susceptible to nonthymidine analogs as well. And though d4T does more toxic damage than AZT, both drugs have ineluctable short- and long-term side effects.

Maybe what’s really needed is a thymidine analog less toxic than either current option. But none seems near the pharmacy shelf. So clinical researchers still spend lots of time sorting the merits and demerits of thymidines and non-thymidines.

Naa Torshie Annan (Chelsea and Westminster Hospital, London) cast an intriguing retrospective look at 723 treatment-naive people starting EFV and 271 starting NVP with two NRTIs [abstract WePe12.2C03]. The Chelsea and Westminster team mounted this study to disentwine potential confounders in cohort analyses comparing the two NNRTIs (which favored EFV) and the randomized 2NN study (which saw no difference). An analysis adjusted for such confounders and stratified by year, viral load, and NRTI backbone found a 27% lower likelihood of virologic success (<500 copies/mL after 12 weeks of treatment) with NVP than with EFV (P = 0.002).

But, 2NN or no 2NN, most prescribers probably favor EFV at this pass, so the study’s more valuable findings may involve backbone differences. A plurality of enrollees, 48%, started with AZT/3TC, while the next most popular spinal specimens were ddl/d4T in 13% and d4T/T3C in 12%. Picking the popular AZT/3TC duo as the comparison backbone (relative hazard [RH] 1.0), Annan found a significantly better chance of virologic success with the thymidine-containing d4T/T3C and a significantly lower chance with non-thymidine mixes:

- d4T/T3C versus AZT/3TC: RH for virologic success 1.52 (95% CI 1.17 to 1.97), P = 0.002
- Nonthymidine twosomes versus AZT/3TC: RH for virologic success 0.62 (95% CI 0.48 to 0.80), P < 0.001

On top of that, the now-notorious non-thymidine pairing of ddl/TDF proved the only significant predictor of treatment failure. Compared with AZT/3TC, ddl/TDF made failure 6.48 times more likely (95% CI 3.81 to 11.0) (P < 0.001).

Of course cohort studies have their own blind spots because they lack randomization. Chelsea and Westminster physicians clearly lean toward EFV, prescribing it almost three times more often than NVP. Yet the proportion of women starting NVP significantly exceeded the proportion of men (P < 0.001). And the NVP group began treatment with a significantly lower viral load (P < 0.001) and a higher CD4 count (P = 0.054).

Three Chelsea and Westminster physicians published a nice exegesis of the ddl/TDF saga just after the conference, concluding that this dyad’s convenience and relative safety vanish in the pitchy shadow of CD4 depletion and a high virologic failure rate when combined up front with NNRTIs. Tenofovir/ddl may be a better bet with RTV-boosted PIs and in people with treatment experience, they suggest, but they cite cohort data documenting pancreatic toxicity and high glucose in people taking such regimens.

A cohort study posted in Rio concurred that ddl/TDF looks reasonable when linked to a PI, especially in simplification regimens [abstract WePe12.9C07]. But which PI you use may make a difference.

M. Olmo (Hospital de Bellvitge, Barcelona) and colleagues in three other Spanish hospitals studied 517 people starting ddl/TDF from January 2002 through June 2004. Only 33 were treatment-naive, while 163 had an undetectable viral load with another regimen and switched to ddl/TDF to make pill taking simpler. Another 148 people made ddl/TDF part of a first or second rescue regimen, and 173 took the NRTIs as part of a third or later rescue combo.
In simplifying regimens ddI/TDF performed equally well with a PI or an NNRTI (Table 6). But PIs handily outdid NNRTIs with ddI/TDF in starting and rescue regimens. Whereas 8.7% taking ddI/TDF with LPV/RTV in rescue regimens experienced virologic failure, 28% with another PI as the third rescue drug suffered failure ($P = 0.002$). The other PIs most often used were atazanavir (ATV)/RTV in 16, nelfinavir (NFV) in eight, saquinavir (SQV)/RTV in five, and IDV/RTV in four.

Kaplan-Meier analysis with a median 39 weeks of follow-up data graphed a significantly longer time to failure with ddI/TDF in simplification versus first-line regimens ($P = 0.0007$), simplification versus first- or second-line rescue regimens ($P = 0.0001$), and simplification versus third-line or later rescue regimens ($P = 0.0009$).

A Cox proportional hazards model figured a higher risk of ddI/TDF failure when the third drug was an NNRTI or NRTI rather than a PI, when physicians did not lower the ddI dose, and when they used the drugs in up-front or rescue regimens rather than to simplify suppressive combinations:

- Third drug NNRTI versus PI: failure hazard ratio (HR) 2.735 (95% CI 1.614 to 4.634), $P = 0.0002$
- Third drug NRTI versus PI: failure HR 3.740 (95% CI 2.108 to 6.636), $P < 0.0001$
- ddI dose adjustment versus no adjustment: failure HR 0.644 (95% CI 0.412 to 1.066), $P = 0.053$
- Naive versus simplification: failure HR 2.757 (95% CI 1.048 to 7.258), $P = 0.040$
- First or second rescue versus simplification: failure HR 2.827 (95% CI 1.428 to 5.597), $P = 0.003$
- Third or later rescue versus simplification: failure HR 2.547 (95% CI 1.270 to 5.109), $P = 0.008$

Picking up TAMs with a first regimen lowered the chance of second-line success in a single-center retrospective study of 97 people by Franco Maggiolo (General Hospital, Bergamo, Italy) [abstract WePe4.4C09]. But in a multivariate analysis, using a thymidine analog in the first regimen did not dim prospects for successful rescue therapy.

These 97 people, 64% of whom acquired HIV heterosexually, had a mean CD4 count of 314 cells/mm$^3$ and a mean viral load of 16,714 copies/mL when their first antiretrovirals pooped out. Maggiolo did not report the numbers taking a first-line thymidine analog, PI, or NNRTI. But all were taking purportedly potent regimens.

Defining second-line response as a viral load below 400 copies/mL six months after starting a new regimen, Maggiolo reckoned a failure rate of 61.5% in people with TAMs versus 33.8% in the TAMless ($P = 0.02$). Whereas 66.2% without TAMs from their first regimen had success with their second, only 38.5% with TAMs notched a sub-400-copy viral load the second time around.

But a multivariate analysis sequestered no independent predictors of second-line success, including use of a thymidine analog or any other antiretrovirals in the inaugural concoction. Nor did the TAM pattern (mutations at codons 41, 210, and 215 versus 67, 70, and 219 versus mixed patterns) help separate second-line responders from nonresponders.

In another study, Maggiolo eyed three poppers earlier lowers the risk of traditional opportunists and the spectral coincidence of the HIV and hepatitis virus epidemics. Yet liver failure counts as a “non-AIDS death.” Massimo Puoti (University of Brescia, Italy) came to Rio with evidence that starting antiretrovirals earlier lowers the risk of liver failure and other non-AIDS deaths [abstract WePe12.2C29].

Puoti tracked mortality in 809 members of his Brescia cohort, defining non-AIDS death as death without a

<table>
<thead>
<tr>
<th>Table 7. Six-month response to three once-daily first-line regimens</th>
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<tr>
<td>ddI/3TC/EFV</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>&lt;50 copies/mL (LOCF) (%)</td>
</tr>
<tr>
<td>&lt;50 copies/mL (as treated) (%)</td>
</tr>
<tr>
<td>Virologic failure, n (%)</td>
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LOCF = last-observation-carried-forward analysis.
Source: Franco Maggiolo, abstract WePe12.2C04.
major opportunistic infection or cancer. Through three years of follow-up he counted 91 such deaths, about half due to liver disease. Nearly one third of all deaths could not be tied to AIDS.

A multivariate model determined that a single risk factor for liver injury independently raised the odds of non-AIDS mortality 2.87 times ($P = 0.0016$). Compared with starting treatment at a CD4 count under 200 cells/mm$^3$, starting with 201 to 349 cells/mm$^3$ trimmed the non-AIDS death risk 10%, a nonsignificant improvement ($P = 0.39$). Starting antiretrovirals with more than 350 cells/mm$^3$ made a non-AIDS death 15% less likely ($P = 0.03$)—independent of liver disease.

Even if antiretroviral-induced toxicity poses stern challenges in managing HIV disease, Puoti concluded, starting treatment before CD4 tallies sink below 350 cells/mm$^3$ apparently makes liver-related and other non-AIDS deaths less—not more—likely.

Intensifying and disintensifying

Two perdurable questions about antiretroviral strategizing still lack good answers:

- When should you intensify a less-than-ideal regimen? And when can you disintensify a good one, opting for simpler maintenance therapy instead?

Kimberly Smith (Rush Presbyterian Medical Center, Chicago) and US AIDS Clinical Trials Group (ACTG) mates faced up to the first question in a 48-week trial of add-on TDF plus a PI switch to LPV/RTV [abstract WePe16.7B06]. The earlier ACTG protocol 375 showed that even long-term viral control below the 100-copy mark does not correct faulty responses to antigens, completely defuse frenzied immune cells, or hoist CD4 counts into normal domains. So Smith and colleagues planned protocol A5136 to see if intensifying an already-good regimen would restore immunologic order.

All 17 study participants had a viral load below 1,000 copies/mL on a PI regimen started during ACTG 315. To ratchet up antiviral vim, Smith added the nucleotide RT inhibitor TDF and switched everyone’s PI to LPV/RTV. Seven of these 17 people had at least one RNA reading above 100 copies/mL during 48 weeks of follow-up, while 10 kept their viral load under 50 copies/mL—and six ended up with fewer than 10 copies/mL.

These 10 responders started their first PI with a median CD4 count of 190 cells/mm$^3$ (range 121 to 233 cells/mm$^3$) and a median load of 89,798 copies/mL (range 39,192 to 265,330 copies/mL). Before intensification their CD4 counts ranged from 405 to 774 cells/mm$^3$ and all had a sub-50 viral load.

During 48 weeks of intensification the median CD4 count of the 10 sub-50 responders edged up from 553 to 584 cells/mm$^3$, a significant change ($P = 0.0078$) that may have less clinical significance. This CD4 gain reflected a jump in memory T cells, as naive T lymphocytes trickled away. Smith speculated that a tired thymus failed to mint fresh CD4 cells in these long-infected people.

CD4 percent, CD8 count, and CD8 percent changed little after shifting to LPV/RTV and adding TDF. In nine people tested, apoptosis dropped significantly. Intensified therapy did nothing to drain latent T-cell reservoirs.

Smith concluded that intensified therapy in people with long-term viral control “may lead to improvements in total CD4 lymphocyte recovery primarily via restoration of memory cells.” But it’s important to remember that only 10 of 17 people (59%) ever kept their plasma load below 50 copies/mL for at least three months with boosted IDV and two NRTIs—then stopped the NRTIs, Central nervous system (CNS) T-cell lymphoma struck one person, who committed suicide 32 weeks after scaling back his regimen; the other 11 maintained sub-50 loads through a median 78 weeks of follow-up, despite occasional blips.

Vernazza made “special efforts” to keep adherence high and checked IDV levels for hints of toxicity. Still, four people paid the price of continuing IDV/RTV with renal toxicity, including three kidney stone bouts and two cases of creeping creatinine. Dropping NRTIs for 48 weeks did not improve DEXA-checked fat abnormalities. Despite the CNS-and-semen rationale for using IDV, Vernazza did not list spinal fluid or seminal HIV loads in his report on this trial.

But he did relay CNS and seminal findings in his Rio report on ATV/RTV, and the news wasn’t great. As in the IDV/RTV trial, everyone in this study had kept HIV in check below the 50-copy mark with a traditional regimen (for a median 9.4 months), and none had a treatment failure on their chart. Everyone started ATV/RTV (300/100 mg daily) and stopped their NRTIs.

Among 24 people who finished 24 weeks of boosted monotherapy, Vernazza...
counted two failures: One person dropped out at week 20, and one had an outright virologic failure at week 8. This second person then confessed failure of an earlier regimen—a protocol violation. Of course in routine practice, more than one person may blur the truth about earlier failures if they want to try something that looks easier.

Of 15 seminal samples checked before monotherapy, two had an RNA load topping 100 copies/mL. Two of 12 checked at week 24 still had detectable RNA in semen. Two of five cerebrospinal fluid samples audited at baseline had RNA readings above 100 copies/mL, as did two of 12 checked at week 24. So it seems ATV/RTV has a tough time scouring HIV from semen and spine fluid.

Vernazza didn’t randomize his IDV/RTV or ATV/RTV trials, but José Arribas (La Paz Hospital, Madrid) did mount a random comparison of LPV/RTV maintenance therapy and continued triple therapy in the so-called OK Study of 42 people with viral loads under 50 copies/mL, for more than six months and no PI failures in their record [abstract WePe12.3C05 and WePe12.3C06]. Monomaintenance didn’t work for four people, but continued triple therapy permitted no viral breakthroughs.

The maintenance group started the trial with two statistically nonsignificant advantages:

- Median (IQR) months under 50 copies/mL: 28.6 (11.3 to 44.9) maintenance versus 15.7 (8.6 to 27.5) continued triple therapy
- Median (IQR) CD4 count: 662 (446 to 740) cells/mm³ maintenance versus 585 (331 to 721) cells/mm³ continued triple therapy

After 48 weeks of follow-up, Arribas tallied three virologic failures (two loads above 500 copies/mL) in the LPV/RTV monomaintenance group and none with steady triple therapy. One person dropped out of the maintenance arm with a detectable load attributed to poor adherence (and more on this below), while high lipids knocked one person out of the three-drug control group.

Those numbers translated into intent-to-treat success rates of 81% with LPV/RTV maintenance and 95% with standard therapy. Three other people in the LPV/RTV mono arm blipped above 50 copies/mL, compared with one in the control group. Primary PI mutations did not pop up during rebounds or blips, and all rebounders reharnessed HIV after resuming their NRTIs.

Probably because PIs are the prime culprits in out-of-line lipids, stopping NRTIs did nothing to improve lipid profiles in this study. The two study groups had no significant lipid changes or differences 48 weeks after randomization.

Analyzing reasons for virologic failure in this trial, Federico Pulido (Doce de Octubre Hospital, Madrid) found two—briefer viral control before randomization and (surprise!) shaky adherence. The four people with viral breakthroughs on solitary LPV/RTV spent a median 40 weeks (IQR 30 to 84 weeks) under 50 copies/mL before randomization, compared with 132 weeks (IQR 40 to 331 weeks) in the constant suppressors (P = 0.02).

Adherence findings, based partly on the GEEMA adherence questionnaire and partly on prescription refills, undermine contentions that people find it easier taking one drug than taking three. The 17 people with steady sub-50 control had a median zero days without medication during the trial, compared with three days in the rebounders (P = 0.008). Median missed doses in the week before a clinic visit measured zero in the constant responders and three in the breakthrough group (P = 0.013).

Pulido also saw a marked trend toward better adherence by drug refill score in the steadily suppressed group (94% versus 70%, P = 0.14). Three of the four people with breakthrough viremia had refill scores of 59%, 60%, and 70%. Scaling back to a one-drug regimen apparently made these people more forgetful or more reckless. The fourth person whose RNA rebounded during monotherapy had perfect adherence by this score—a finding that either shows the limits of refill scores or suggests some still-undiscovered reason for that rebound.

Rather than featuring these insightful analyses in a slide session, the Rio conference’s science panel elected to favor yet a third look at this trial, perhaps the least important of the three. Using a rejiggered Roche Laboratories assay that can spot three RNA copies/mL, John McKinnon (University of Pittsburgh) retested plasma samples from the LPV/RTV mono and control arms [abstract WeOa0203]. Median loads reckon with this test didn’t differ between study groups at any point in the trial, but the four people with viral breakthroughs certainly tugged up their group’s median. In these four McKinnon picked up the first hints of recrudescent RNA eight weeks after randomization, a sibylline bubble that

### Table 8. CD4 changes with 1.5 or 3.0 mg of growth hormone

<table>
<thead>
<tr>
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<th>Week 24</th>
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<th>Week 48</th>
<th></th>
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<tbody>
<tr>
<td>Total CD4 count (cells/mm³), 1.5 mg</td>
<td>+19</td>
<td>0.03</td>
<td>+36</td>
<td>0.001</td>
</tr>
<tr>
<td>Total CD4 count (cells/mm³), 3.0 mg†</td>
<td>+16</td>
<td>0.16</td>
<td>+55</td>
<td>0.001</td>
</tr>
<tr>
<td>Naive CD4 count (cells/mm³), 1.5 mg</td>
<td>+4</td>
<td>0.04</td>
<td>+26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Naive CD4 count (cells/mm³), 3.0 mg†</td>
<td>+5</td>
<td>0.20</td>
<td>+23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Naive CD%, 1.5 mg</td>
<td>No change</td>
<td>0.5</td>
<td>+8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Naive CD%, 3.0 mg†</td>
<td>-2%</td>
<td>0.07</td>
<td>+4%</td>
<td>0.003</td>
</tr>
<tr>
<td>Recent thymic immigrants (log copies/mL), 1.5 mg</td>
<td>-0.03</td>
<td>0.57</td>
<td>+1.08</td>
<td>0.03</td>
</tr>
<tr>
<td>Recent thymic immigrants (log copies/mL), 3.0 mg†</td>
<td>+0.33</td>
<td>0.22</td>
<td>+0.48</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Compared with baseline. †Treatment with 3.0 mg began at week 24.

Source: Kimberly Smith, abstract TuOa0203.
popped above the 50-copy surface around week 32.

Physicians who run these studies always close by warning against mono-maintenance in practice. And one hopes the array of risks portrayed in these results will temper enthusiasm for this tactic. Yet reports on boosted PI monotherapy almost always accentuate the positive—and rarely the negative. But one could argue the negatives matter more when testing a risky—and perhaps gratuitous—strategy.

**CD4 spurts with growth hormone**

Recombinant growth hormone did great as a remedy for AIDS wasting, but it always received mixed marks as a tonic for truncal fat: the hunt is still on for a tolerable long-term dose. But three reports in Rio thrust growth hormone into a new role—a CD4 booster that may prick up HIV-specific immune responses.

Two years ago Mike McCune’s Gladstone Institute team showed in a pilot study that six to 12 months of growth hormone reversed thymic shrinkage in five HIV-infected adults and inflated quotients of critical naive CD4 cells. The same researchers, an ACTG troupe, and a London team offered results of bigger, randomized trials at the Rio conference, and the returns remained positive.

The ACTG effort randomized 55 men and five women to add 1.5 mg of recombinant growth hormone daily to their antiretrovirals for 48 weeks or to continue antiretrovirals for 24 weeks and then add 3 mg of growth hormone daily for the next 24. Everyone had tight viral control with sub-50-copy viremia for more than one year. Study participants started the trial with a mean CD4 count of 230 cells/mm³ (IQR 161 to 300 cells/mm³). Median age was 47 years in the 1.5-mg arm and 48 years in the 3-mg arm.

Rush Presbyterian Medical Center’s Kimberly Smith reported that eight people stopped growth hormone before the study ended, six of them (10% overall) because of carpal tunnel syndrome and two for reasons unrelated to the drug [abstract TuOa0203]. Grade 3 or 4 side effects cropped up in seven people taking 3 mg and four taking 1.5 mg, while seven in the 1.5-mg group and five in the 3-mg group had grade 3 or 4 lab skews (including three triglyceride jumps with 1.5 mg).

The 1.5-mg dose started adding naive and total CD4 cells right away, while little changed in the 3-mg delayed-treatment group (Table 8). Then, when the 3-mg group started growth hormone at week 24, it caught up with the 1.5-mg arm in CD4 gains. A CT scan substudy showed a growing thymus in seven of 11 people taking 1.5 mg (P=0.06) and seven of nine taking 3 mg (P=0.016) for 24 weeks.

The CT evidence that growth hormone pumps up the thymus, coupled with significant gains in naive CD4 cells and recent thymic immigrants, suggests the drug turns a rusty, HIV-addled thymus into a perky T-cell turbine.

Laura Napolitano (Gladstone Institute, San Francisco) devised a more complex trial scheme, randomizing 10 adults (group 1) to 3 mg of growth hormone for six months then 1.5 mg for another six months, and nine people (group 2) to one year of observation without growth hormone [MoPpLB0104]. In the second year, the untreated group injected 3 mg of growth hormone for six months and 1.5 mg for another six while the already treated people became untreated controls. Her Rio report covered year-1 results.

Group 1 was slightly older (median 54 versus 48 years, P=0.49) and had a marginally higher CD4 count (median 230 versus 178 cells/mm³, P=0.21). The groups matched exactly in median time on stable antiretroviral therapy (2.7 years), median viral load (75 copies/mL), and median thymus score (1.0).

In the study’s first year, thymus score, density, and volume all burgeoned in the treated group but stayed flat or shrunk in untreated controls. The thymus score climbed 1.51 with growth hormone and dropped 0.02 without it (P=0.004). These findings mirror results in the ACTG trial. Total CD4 cells rose 19% with growth hormone (P=0.093) and naive CD4s 69% (P=0.0002) with growth hormone, but naive CD8 cells did not. Napolitano suggested the discrepancy between naive CD4 and CD8 gains could mean some CD8s may have a font outside the thymus.

Side effects proved even more problematic in this trial than in the ACTG study, perhaps because everyone started with 3 mg daily. Four of 10 people gave up on growth hormone—one with diabetes diagnosed after one month, one with carpal tunnel syndrome after six months, one with fatigue after seven months, and one with hand pain after nine months. On top of that, six people temporarily suspended treatment or stepped down to the lower dose early because of glucose intolerance, arthralgias, or carpal tunnel syndrome.

In a third trial, Nesrina Imami (Imperial College, London) and colleagues at Chelsea and Westminster Hospital gave 4 mg of growth hormone daily for 12 weeks to 12 people with a CD4 count above 200 cells/mm³ and well-controlled viremia [abstract WePe16.7B01]. For the next 12 weeks they got evenly randomized to placebo, 4 mg every other day, or 4 mg twice weekly.

Proliferative CD4-cell responses and levels of interferon-γ-producing CD8 cells rose significantly during the 12 weeks of daily therapy. Before growth hormone therapy only one of 12 study participants had evidence of HIV-specific CD4...

<table>
<thead>
<tr>
<th>Incidence of thyroid disease before and with HAART</th>
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<tr>
<td>Disease</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Hypothyroidism</td>
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<td>Hyperthyroidism</td>
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Source: P. Sen, abstract TuPe2.3C09.
First the Chelsea and Westminster team parsed files of everyone in the HIV clinic treated with thyroid meds between April 1995 and June 2004. They turned up 25 cases of hypothyroidism and eight cases of hyperthyroidism in people with a median CD4 count of 228 cells/mm³ (IQR 156 to 325 cells/mm³). Diagnosis of hypothyroidism jumped 10-fold in the potent antiretroviral era, while hyperthyroidism incidence ballooned 8.5-fold (Table 9).

Meanwhile, diligent Chelsea and Westminster physicians screened 2,437 HIV-infected people for thyroid dysfunction, finding it in 54. The clinic’s prevalence of hypothyroidism measured 1.2% and of hyperthyroidism 1.01%. Hypothyroidism proved significantly more prevalent among people currently taking a PI ($P = 0.025$), while NNRTIs seemed linked to hyperthyroidism ($P = 0.002$).

CD4 count did not correlate with a sputtering thymus in these analyses. Sen and colleagues believe their findings justify routine thyroid function testing for people taking antiretrovirals, especially PIIs or NNRTIs.

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

Acknowledgment
Thanks to Alan MacRobert, Senior Editor of Sky & Telescope, for his deft explanation of why night falls fast in the tropics. See note 1.

Editor’s Note: See the December 2005 issue of the IAPAC Monthly for Part 2 of this article, which will analyze news on second-line regimens, treatment interruptions, antiretroviral toxicities, and HIV-related coinfections.

References and Notes
1. Alan MacRobert, Senior Editor of Sky & Telescope (http://www.skyandtelescope.com), explained via e-mail that night falls fast in the tropics because, at those latitudes, the sun moves more or less straight down as it sets. At high latitudes, as in Europe and the United States, the sun moves diagonally downward, at a shallower angle. The shallower angle means the sun takes longer to reach a given distance below the horizon, and that prolongs the twilight after sunset in northern lands.
2. Sugar loaf and similar stranded spires are inselbergs, from the German for “island mountains.” Inselbergs appear, according to the Encyclopaedia Britannica, because their tough plutonic rock (typically granite or gneiss) resists erosion. Polo’s inselbergs are remnants of the Serra do Mar, a primeval gneiss-granite mountain chain.
3. It doesn’t.
10. Chin Ho-Ping PV, Deeks SG, Liegel T, et al. Methamphetamine use is associated with ongoing high-risk sexual behaviours among HIV-infected individuals with drug-resistant HIV. Antivir Ther. 2005;10(suppl 1):S130. Abstract 117. This prospective study of 189 antiretroviral-treated people with detectable viremia and at least one resistance mutation found that methamphetamine use independently quadrupled the risk of unprotected sex with a partner who did not have HIV or had an unknown serostatus. Sidelnick nearly quadrupled that risk.
17. van Leth F, Phanuphak P, Ruxrungtham K, et al. ZNFN1A comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomized open-label trial, the ZNN Study. Lancet. 2004;363:1253-1263.
ABSTRACTS

Journal of Infectious Diseases

CD4 lymphocyte percentage predicts disease progression in HIV-infected patients initiating highly active antiretroviral therapy with CD4 lymphocyte counts >350 lymphocytes/mm³


BACKGROUND: The optimal timing of highly active antiretroviral therapy (HAART) in human immunodeficiency virus (HIV)-infected patients with ≥200 absolute CD4 lymphocytes/mm³ is unknown. CD4 lymphocyte percentage could add prognostic information. METHODS: Persons who initiated HAART between January 1, 1998, and January 1, 2003, received ≥30 days of therapy, and had baseline CD4 lymphocyte data available were included in the study. The log-rank test for time to event and Cox proportional hazards models were used to determine predictors of a new acquired immunodeficiency syndrome (AIDS)-defining illness or death. RESULTS: A total of 788 patients met the inclusion criteria. At baseline, subjects had a median of 225 CD4 lymphocytes/mm³ and 17% CD4 lymphocytes. Subjects with ≥17% CD4 lymphocytes had earlier disease progression, compared with subjects with ≥17%, both in the entire cohort (P = 0.0001) and of those subjects with >350 absolute CD4 lymphocytes/mm³ at baseline (P = 0.03). CD4 lymphocyte percentage ≥17% was the strongest predictor of disease progression among subjects in this latter group (hazard ratio [HR], 3.57; 95% CI, 2.6-38) were associated with AIN after adjustment for length of time participants were HIV-positive, CD4 count and HIV viral load. CONCLUSIONS: The prevalence of AIN has remained high among HIV-positive MSM after the introduction of HAART. Our data indicate that HAART is not associated with a reduced prevalence of AIN, and support measures to prevent anal cancer among HIV-positive MSM whether or not they are using HAART.


Medical Care

Hospital and outpatient health services utilization among HIV-infected adults in care (2000-2002)


BACKGROUND: Rapid changes in HIV epidemiology and antiretroviral therapy may have resulted in recent changes in patterns of health care utilization. OBJECTIVE: The objective of this study was to examine sociodemographic and clinical correlates of inpatient and outpatient HIV-related health service utilization in a multistate sample of patients with HIV. DESIGN: Demographic, clinical, and resource utilization data were collected from medical records for 2000, 2001, and 2002. SETTING: This study was conducted at 11 US HIV primary and specialty care sites in different geographic regions. PATIENTS: In each year, HIV-positive patients with at least one CD4 count and any use of inpatient, outpatient, or emergency room services. Sample sizes were 13,392 in 2000, 15,211 in 2001, and 14,403 in 2002. MAIN OUTCOME MEASURES: Main outcome measures were number of hospital admissions, total days in hospital, and number of outpatient clinic/office visits per year. Inpatient and outpatient costs were estimated by applying unit costs to numbers of inpatient days and outpatient visits. RESULTS: Mean numbers of admissions per person per year decreased from 2000 (0.40) to 2002 (0.35), but this difference was not significant in multivariate analyses. Hospitalization rates were significantly higher among patients with greater immunosuppression, women, blacks, patients who acquired HIV through drug use, those 50 years of age and over, and those with Medicaid or Medicare. Mean annual outpatient visits decreased significantly between 2000 and 2002, from 6.06 to 5.66 visits per person per year. Whites, Hispanics, those 30 years of age and over, those on highly active antiretroviral therapy (HAART), and those with Medicaid or Medicare had significantly higher outpatient utilization. Inpatient costs per patient per month (PPPM) were estimated to be US$514 in 2000, US$472 in 2001, and US$424 in 2002; outpatient costs PPPM were estimated at US$108 in 2000, US$100 in 2001, and US$101 in 2002. CONCLUSION: Changes in utilization over this three-year period, although statistically significant in some cases, were not substantial. Hospitalization rates remain relatively high among minority or disadvantaged groups, suggesting persistent disparities in care. Combined inpatient and outpatient costs for patients on HAART were not significantly lower than for patients not on HAART.


BMC Infectious Diseases

Safety and tolerability of nevirapine-based antiretroviral therapy in HIV-infected patients receiving fluconazole for cryptococcal prophylaxis: A case-control study

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BACKGROUND: To compare the adverse events after initiation of nevirapine (NVP)-based antiretroviral therapy (ART) among HIV-infected patients who did not receive fluconazole (group A), received fluconazole 400 mg/week (group B), and received fluconazole 200 mg/day (group C). METHODS: A retrospective cohort study was conducted among HIV-infected patients who began NVP-based ART between December 2003 and September 2004. Patients were followed up for six months. Clinical hepatitis, elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (> 3 times from baseline), and skin rashes were studied. RESULTS: There were 686 patients; 225, 392, and 69 patients in groups A, B, and C, respectively. Baseline characteristics including age, previous opportunistic infections, use of antituberculous drugs, and baseline aminotransferase levels among the three groups were similar. Group C had a higher proportion of men (P = 0.016). Baseline median (interquartile range [IQR]) CD4 counts were 85 (21-159), 18 (7-48), and 16 (5-35) cells/mm³ in groups A, B, and C, respectively (P < 0.001). Two of 225 (0.9%), four of 392 (1.0%), and zero of 69 (0%) patients in groups A, B, and C developed clinical hepatitis (P = 0.705). There was no significant difference in elevated AST or ALT among the three groups (P > 0.05). By logistic regression, receiving fluconazole was not predictive of clinical hepatitis, elevated aminotransferase, or skin rashes. At six months after initiating NVP, 174 (77.3%) patients in group A, 309 (78.8%) patients in group B, and 58 (84.1%) patients in group C remained on NVP. CONCLUSION: Initiation of NVP-based ART among Thais with advanced HIV disease receiving fluconazole is safe and well tolerated. Nevirapine should not be contraindicated for patients receiving fluconazole for treatment or prophylaxis of cryptococcosis.

Michael Carter

Treatment with lopinavir/ritonavir (LPV/r) does not involve a high rate of major liver side effects, according to an Italian study published in the September 2, 2005, edition of AIDS. The investigators found that even though over 40% of the patients enrolled in their study were coinfected with hepatitis B virus (HBV) or hepatitis C virus (HCV), the incidence of a grade III or IV liver abnormality was less than one per 100 person years of follow-up.

Since the advent of antiretroviral therapy (ART), liver-related illness has emerged as a major cause of illness and death among HIV-positive patients. This is because of the high rate of viral hepatitis coinfection among HIV-positive patients and the hepatotoxicity which some drugs in each of the three main classes of antiretroviral drugs can cause.

Studies suggest that between 2% and 11% of patients taking LPV/r will develop severe hepatotoxicity. Italian investigators used data obtained from an online reporting system for severe side effects caused by antiretroviral drugs (the SCOLTA project) to determine the incidence of severe (grade III and IV) liver-related side effects in 755 patients treated with LPV/r.

A total of 44% of patients were coinfected with HBV or HCV, and the mean period of observation was 17 months. The total incidence of severe adverse events was 11 per 100 patient years of follow-up. There was a lower incidence of severe side effects among treatment-naive patients (7 per 100 person years) compared to treatment-experienced patients (12 per 100 person years). The most common side effects were metabolic-related events (5 per 100 person years).

The investigators then examined liver-related side effects. They observed that “hepatic toxicity was not frequent,” with an overall incidence of 0.59 per 100 person years. There was a marginally higher incidence in treatment-naive patients (0.54 per 100 person years) compared to treatment-experienced individuals (0.48 per 100 person years).

One treatment-naive and four treatment-experienced patients experienced severe liver-related events. Four of these patients were coinfected with HCV. Two cases developed shortly after treatment was initiated; the other three after a year of therapy. In all five cases treatment had to be stopped.

“This study comprises the biggest series to date of patients treated with [LPV/r] and followed prospectively outside clinical trials... this HIV-positive population had a high prevalence of coinfection with hepatitis viruses,” the investigators comment. They suggest that the retrospective design of other studies could explain the apparently higher rate of hepatotoxicity found.

Reference
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 Bonaventura Clotet, Head of the Retrovirology Lab “irsiCaixa Foundation” and Head of the HIV Unit in the Hospital Universitari Germans Trias i Pujol, in Badalona, Spain.

**Bonaventura Clotet**

What proverb, colloquial expression, or quote best describes how you view the world and yourself in it? Violence only generates violence.

What activities, avocations, or hobbies interest you? Do you have a hidden talent? I enjoy running, writing novels, and painting.

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

Who are your mentors or real life heroes? Any sincere individual capable of investing part of his or her time and resources to support those who need help.

With what historical figure do you most identify? Mahatma Gandhi.


If you could have chosen to live during any time period in human history, which would it be? The period of Egyptian splendor.

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

In your opinion, what are the greatest achievements and failures of humanity? Greatest achievement: Improvements in health. Greatest failures: Increasing poverty, hunger, and the gap between the rich and poor. Indeed, the lack of protection of the planet.

What is your prediction as to the future of our planet one full decade from present day? Unfortunately, if there is not more investment in protecting the planet, we will observe the planet’s progressive deterioration. ■
The share of the working-age population in sub-Saharan Africa is starting to rise and is projected to increase substantially over the next 40 to 50 years despite the HIV/AIDS pandemic, which has taken a terrible toll on human life in the region.

Excerpt from an International Monetary Fund (IMF) analysis released September 21, 2005, as quoted in an Agence France Presse report. The IMF analysis predicts that despite the toll of HIV/AIDS, sub-Saharan Africa’s working-age population is growing and should continue to do so during the coming 40 years. After falling from 5.4% in 2004 to 4.8% this year, the region’s economic growth should climb to 5.9% in 2006. If that increase is achieved, the IMF notes it would be the strongest economic expansion in sub-Saharan Africa since the early 1970s.

If women and girls are to have a genuine opportunity to protect themselves, their best option is the rapid development of new HIV-prevention technologies like microbicides, which women can initiate.

US Representative Christopher Shays (R-Connecticut) quoted in a September 23, 2005, press release issued by the Alliance for Microbicide Development and the Global Campaign for Microbicides on the occasion of the introduction of the “Microbicide Development Act of 2005” in the US House of Representatives. Introduced by Shays and fellow US Representative Jan Schakowsky (D-Illinois), the bill seeks to establish a Microbicide Research and Development Unit at the US National Institutes of Health (NIH), and strengthen microbicides-related activity at the US Agency for International Development (USAID) and the US Centers for Disease Control and Prevention (CDC).

These approvals will now allow those infected with HIV more access to these life-saving drugs within our country.

Mike Leavitt, US Secretary of Health and Human Services, quoted in a September 20, 2005, Associated Press report about the US Food and Drug Administration (FDA) approval of a generic version of zidovudine (AZT) for the US market. Generic AZT was previously unavailable in the United States because GlaxoSmithKline held the patent for the drug, which was approved by the FDA in 1987. With GlaxoSmithKline’s AZT patent now expired, the FDA approved generic versions of AZT made by the Indian pharmaceutical manufacturers Ranbaxy Laboratories and Aurobindo Pharma, as well as the US-based Roxane Laboratories.

There is a danger if the husband cannot satisfy the wives, they will be tempted to look for sex outside the marriage, or one of the partners may be infected and this will increase the risk of contracting and spreading HIV.

Excerpt from a 23-page document released by leaders of the Vapostori indigenous Christian sects in Zimbabwe, as quoted in a September 18, 2005, Associated Press Report. In what Zimbabwe’s government called a historic breakthrough in the war on AIDS, the religious leaders called on their followers to abandon the practice of polygamy. The leaders also spoke out against child marriage as well as the inheritance of brothers’ widows, both practices that had been previously accepted. Vapostori followers practice a blend of Christianity and African reverence for ancestors, and many disapprove of Western medicine and the education of girls.

After my husband died my parents-in-law threw me out of their house. My brother’s wife didn’t want me in my family’s house either. I had no place to go, that’s why my daughter and I came here.

Nagmani, a 23-year-old woman from the city of Vijayavada in the southern Indian state of Andhra Pradesh, discussing her plight as an HIV-positive Indian woman in a September 21, 2005, BBC News report. India has an estimated 5 million HIV-positive people, 39% of whom are women.

It may be the death knell for [GlaxoSmithKline’s] entry inhibitor.

Martin Delaney, founder of the San Francisco-based Project Inform, quoted in a September 19, 2005, Wall Street Journal article about a GlaxoSmithKline announcement that it had halted safety and efficacy trials of an experimental new drug after two of 250 treatment-naive trial patients developed severe liver toxicity. However, studies of aplaviroc, GSK’s candidate in a new class of drugs known as CCR5 inhibitors, are continuing among a subgroup of 40 HIV-positive patients whose virus is resistant to currently available antiretroviral drugs. GlaxoSmithKline said it halted the study in the treatment-naive subgroup following discussions with the US Food and Drug Administration (FDA).
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