

Prescription for Profits

Veteran NEJM Editor Takes on Big Pharma As No One Before; Calls for Sweeping Reforms

‘Weaning us off the dope’

Just as the hand-wringing PR exercise that has become the international AIDS conference was winding down halfway across the globe, this little item hit the newsstand in the states:

July 15, 2004—Members of a government panel, which earlier this week recommended more aggressive use of statin medications for people at the highest risk of dying from heart disease, failed to disclose financial links to the companies that make the drugs.

The revised consensus guidelines were issued by none less than the American Heart Association and were drawn up by a government panel of experts in the field, convened by the NIH's own National Heart, Lung, and Blood Institute. The new rules, if sustained, would lower serum cholesterol targets to a point where 7 million more Americans would be encouraged to start taking the cholesterol lowering medications of Pfizer, Merck, BMS and AstraZeneca. (At \$3,000 a year and 20-30% margins, we're talking an additional \$4-6 billion a year in profits—with little more than the stroke of a pen.)

New York Newsday first reported

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Party Pooper

I find it hard to imagine that a system this corrupt can be a good thing, or that it is worth the vast amounts of money spent on it. In addition, we have to ask ourselves whether it really is a net benefit to the public to be taking so many drugs. In my view, we have become an overmedicated society.

Marcia Angell, MD, August 2004
The Truth About the Drug Companies: How They Deceive Us And What To Do About It

TDM, ¡Stat!

Más Mezclas Rechazadas Debido A Preocupaciones Por Concentración

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‘Combos locos y explosivos’

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Yasmin Halima y Rob Camp asistieron al Taller de Farmacología de un día de duración que se llevó a cabo inmediatamente después de la Conferencia 2004 sobre Retrovirus. Aquí reproducimos el informe que prepararon acerca de algunas combinaciones locas, por no decir explosivas. Agradecen a todos los presentadores por haber revisado su información.

Statins + HAART

Muchas personas VIH+ están siendo tratadas actualmente con drogas de statin para manejar el aumento de los lípidos. Es esencial comprender las interacciones farmacológicas entre los statins y las drogas de

— sigue en la página 13 —

The Agony of Bangkok

Thai Activist Exhorts Conference Crowd To Stand Firm Against U.S. Patent Regime and ‘Masks of Fake Concern’

‘Trading away health’

The following is the text of an address delivered by Thai AIDS Treatment Action Group director Paisan Suwannawong at the opening ceremony of the 15th International AIDS Conference which took place in Bangkok this summer. Special thanks to Paisan for his permission to reprint.

Good evening, ladies, gentlemen, and friends. Welcome to Bangkok. Sorry if I am a little nervous, but I am not used to speaking on stage; I am more experienced with speaking on the street. First, I would like to say thank you to the people who supported my invitation to speak, and thank you to the International AIDS Society because it means a lot to me to be able to speak here from the perspective of a drug user living with HIV.

I would like to tell you a little bit about myself. I grew up in one of Bangkok's biggest slums, not far from here. I saw many people using drugs, but never imagined that I would become a drug user myself. The first time I smoked marijuana, it felt like a challenge because all the public campaigns said drugs were “bad” and “dangerous.” I found it wasn't true, so I continued to

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 the story in its Thursday edition. Eight of the nine panel members had earned money specifically from cholesterol drug makers, including Pfizer, Merck, BMS and AstraZeneca. The NIH's Dr. James Cleeman and Dr. Rose Marie Robertson, of the AHA, both said they felt financial disclosure had been covered because all but two of the authors had also served on the 2001 consensus panel—and that they had made their industry connections known then.

The summer imbroglia set familiar alarm bells sounding: foxes guarding the hen house, physicians and researchers as pharma skills. Of course, guidelines meddling is among the oldest tricks in the Big Pharma playbook. The wisest, perhaps privileged, clinicians routinely eschew such interference and hope nothing untoward will befall them for their brave and educated insolence. But the fact remains that guidelines of all guises in all specialties whack quite a wallop in establishing prescription patterns and the standard-of-care. And thus, not unlike the Swiftboat veterans' media blitz in swing electoral states, efforts to influence them suck in tens of millions of dollars a pop.

Perhaps due to an historic vigilance among AIDS activists and clinician advocates (or to its infectious nature), the field of HIV medicine has so far been spared the

most egregious of these marketing-masquerading-as-medicine maneuvers. In fact, the two notable revisions to HIV's standard-of-care followed on the heels of therapeutic setbacks (results of the early vs. deferred AZT "Concorde" study, circa 1993; and the failure of the eradication hypothesis, around 1998) and resulted in retrenchment rather than new aggressivity—albeit not without sustained intervention to limit the damage.

But might that portion of the Big Pharma enthralled research and treatment establishment still be clinging onto a model of overmedicization in order to please its industry pimps? After all, the NIH's hallowed Principles of Antiretroviral Therapy seem immune to re-evaluation—even though the science and hypotheses on which they were based have largely been overtaken by events. "It's the virus, stupid" sprang from its en-coffined slumber on the wings of hope—fueled by the rallying cries of medical marketers—and has since taken on a life of its own. But where the silver dagger to return it to its repose?

When otherwise patient friendly researchers and community docs self-satisfyingly state, with all the authority their years of furtive pharma hustling has bought them, before a conference crowd that "lifelong antiretroviral therapy is not really a problem (anymore) because easier to take, less toxic combos are now available or just over the horizon"; when Trizivir and Viread+Sustiva or Kaletra are considered treatment sparing "maintenance" regimens in virtually all the studies pretending to re-explore this approach (see inset, bottom of page 6); when patient advocates on federal panels sign off on (or instigate) sweeping prohibitions which diminish our treatment options and further bottleneck the progress of clinical care; we, my fellow HIVers, activists, clinicians, researchers, need to rediscover our activist rage and imagination.

Pharmaceutical Industry Revenue and Expense Breakdown, 2002†

Research & Development	\$31 billion
Marketing	\$67 billion
Profits	\$36 billion

†Based on total worldwide sales of \$217 billion.

Source: Public Citizen Congress Watch, "2002 Drug Industry Profits: Hefty Pharmaceutical Company Margins Dward Other Industries," June 2003 (cited in M Angell, 2004)

It Wasn't Always Like This
 The Truth About the Drug Companies
 [excerpts]

There used to be something faintly disreputable about really big fortunes. You could choose to do well or you could choose to do good, but most people who had a choice in the matter thought it difficult to do both. That belief was particularly strong among scientists and other intellectuals. They could choose to live a comfortable but not luxurious life in academia, or they could "sell out" to industry and do less important but more remunerative work. One of the results has been a growing pro-industry bias in medical research... and CME programs—exactly where such bias doesn't belong. (page 8)

Many members of the FDA's eighteen **advisory committees** have financial connections to interested companies [see page 7 of this issue]. Although there are conflict-of-interest rules that prohibit participation in such cases, the agency regularly waives them on the unlikely grounds that someone's advice is indispensable. (page 210)

Med ed writers and circuit **speakers** are often paid consultants for the drug companies. They are usually required to disclose financial ties [see page 8 (web version only, of this issue), and that disclosure is supposed to make it acceptable that they have them. But drug companies or their agents, the **MECCs**, often suggest the topic and speaker—and even put together the slides. (page 140)

It's hard to believe that close and remunerative personal ties with drug companies do not add to the strong pro-industry bias in medical research and education. Big pharma not only controls the details of the way clinical trials are performed, but as backup, it also works to win the **hearts and minds** of researchers. (page 104)

Drug companies are extremely generous to doctors in their 'education' activities... Doctors are invited to dinners in expensive restaurants or on junkets to luxurious settings to act as 'consultants' or 'advisors.' The doctors listen to speakers and provide some minimal response about how they like the company drugs or what they think of a new advertising campaign. That enables drug companies to pay doctors just for showing up (\$1,000 a pop for the coveted high prescribers as of August 2004). Participants may also receive training to serve on speakers' bureaus, so that they too can become **company skills**. p141

Such gifts would trigger a red **bribery alert** in the mind of just about any public official or government contractor. But not, it seems, in the minds of many doctors. (page 128)

Why do **doctors** pretend they believe drug companies are interested in education? (Some of them actually believe it.) The answer is: It pays. Doctors would lose the travel and entertainment and other emoluments too many of them have come to believe are **entitlements** to their profession. Many doctors become **indignant** when it is suggested that they might be swayed by all this industry largesse. But why else would drug companies put so much money into them? (page 147)

One of the more sobering indications of the extent to which big pharma has compromised the research community is its extensive inroads into the **NIH** itself. (page 103)

“How to Save the Pharmaceutical Industry—And Get Our Money’s Worth”

Seven broad problems:

1. Too many me-too drugs and too few innovative ones.
2. Key information about R&D, marketing and pricing is kept secret.
3. Drug companies have too much control over clinical research on their own products.
4. Drug companies control medical education about their own products.
5. The FDA is too much “in thrall” of the industry it is supposed to regulate.
6. Patents and other exclusive marketing rights are too long and too elastic.
7. Prices are too high and too variable.

Seven key reforms:

1. Shift the emphasis from me-too to innovation.

- U.S. patent law should be enforced in its original form.

2. Strengthen the FDA.

- Repeal the Prescription Drug User Fee Act (or allow it to expire in 2006).
- Increase public funding for the agency.
- Exclude experts with financial ties to industry from the FDA’s advisory committees.

3. Create an institute to oversee clinical trials.

4. Curb monopoly marketing rights.

- The clock on patents should not begin ticking until the drugs come to market.
- The loopholes in the Hatch-Waxman Act should be closed so that exclusivity cannot be stretched out for years.

5. Get Big Pharma out of medical education.

- Once and for all, we should clarify a simple fact: Drug companies are not providers of education—and they *cannot be*.
 - No laws, regulations, or guidelines should be based on the idea that they are.
 - The medical profession needs to take full responsibility for educating its members just as other professions do.

There are a few simple steps to make this happen:

- 1) Medical schools should teach students about drugs, not leave such education to industry-sponsored programs and teaching materials.
- 2) Teaching hospitals should regard drug [.] reps just as they do other salespeople (who are not allowed to traipse around at will, promoting their wares and offering gifts and meals to medical students and doctors in training.)
- 3) The profession needs to take responsibility for continuing medical education (CME). Just as there should be no private clinical research industry, there should be no private medical education industry hired by the drug companies.
- 4) Professional associations need to be self-supporting.
- 5) Direct-to-consumer advertising should be prohibited in the United States—just as it is in other advanced countries.

6. Open the “black box” of R&D and marketing costs.

- The pharmaceutical industry should be regarded as a public utility: its books should be open.

7. Establish reasonable and uniform pricing.

- Drug prices should be not only transparent but reasonable and as uniform as possible for all purchasers.
- President Bush’s Medicare reform bill (2003) should be *repealed* and replaced by a simple measure that guarantees all Medicare beneficiaries appropriate coverage of their drug costs, with government-negotiated payments to industry and a medically based formulary.

Source: Angell M, “The Truth About the Drug Companies: How They Deceive Us and What to Do About It,” (Random House, 2004)

The field of HIV/AIDS seems poised, once again, at a crossroads. Only this time activism and advocacy are deafening only in their silence. While the black and white, demagogic issues such as Abbott’s notorious price gouging

rampage had even the bloated pharma front men crying foul, the more insidious issues—an anachronistic treatment paradigm, a research and regulatory establishment high-jacked by industry—go entirely unaddressed. It is with-

in this context that an important voice may have serendipitously risen to stimulate our latent activist memory cells: former NEJM editor Marcia Angell via her gutsy deconstruction of (nearly) all that ails us.

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Marcia Angell wasn't always a crusader. Some may remember her rather uncritical endorsement of the design and conduct of the seminal AZT study (at 1,500 mg a day; it's now dosed at 600—and 500 mg or less, outside the U.S.) when it appeared in the pages of her little journal, circa 1987. Others haven't forgiven her her tough stance against alternative medicine. But with the release of her new book late last month, "The Truth About the Drug Companies: How They Deceive Us and What We Can Do About It," Dr. Angell appears to have Goliath precariously centered within the cross hairs of a populist sling shot; her rousing philippic having transformed an otherwise mild mannered Harvard lecturer into a present day Daniel J. Goldhagen of the medical profession.

She clearly doesn't buy the Nussbaumian "good intentions" defense; instead, she lays out the evidence like an expert prosecutor—and goads us all to cease the charade. For those among us who, over the years, have come to rely on drug company beneficence for little luxuries here and there (and maybe even some extra pocket money), implementation of the Angell agenda will not be painless. Her clear and cogently articulated vision is of a reformed medical profession as much as it is a reformed pharmaceutical industry—both of

which need to return to their mission, she argues, of serving the public interest.

Angell's epiphanal moment is said to have occurred in the spring of 2000 when newly required conflict-of-interest disclosures for authors exceeded the available page space. The study in question was of an antidepressant drug, nefazodone, developed by Bristol-Myers Squibb. All but one of the study investigators reported consultancy arrangements, speaking honoraria, and membership on pharma advisory boards—in most cases, with pharma companies producing similar types of drugs. Visibly frustrated, Angell referred readers to the journal's website for the complete list of pharma financial entanglements. In disgust, she penned a now legendary accompanying editorial for the issue, "Is Academic Medicine for Sale?"

If we have become inured to apocryphal tales such as that of the section chief who supplemented his income to the tune of \$500,000 a year through pharma consulting gigs or the clinical trials sites paid \$12,000 per patient enrolled—with a \$30,000 bonus if the number reaches six, Angell's manifesto threatens to shake us from our stupor. And in a hodge-podge effort to depict the HIV KOLs and consensus makers in this regard, two extra pages of TAGline's back-to-school issue are dedicated Dr. Angell, in support of her campaign to bring medicine back to the people and to save Big Pharma from its most egregious excesses.

Early reviewers of the data note that acceptance of financial goodies (not to mention the unquantifiable triumvirate of fame, friendship and flattery) is not in itself evidence of objectivity's loss. In fact, without exception, the half dozen or so New York City HIV docs informally queried about their advisory and lecture circuit relationships with Big Pharma were

eager to point out that they moonlighted for "all the major drug companies" with HIV products expressly "to avoid any question of bias." Others note that Angell's scorched earth solution (barring anyone with pharma ties from key panel posts) would only be self-defeating. Were financial ties to drug companies an automatic disqualifier, the argument goes, there'd be only empty chairs at empty tables. (Angell disagrees.)

For the time being, the only remedy deemed workable is that of disclosure requirements—ironically, what appears to have sparked Angell's fiery exposé in the first place. But, as she is quick to point out, does the mere act of disclosing financial ties to industry then render them acceptable? In the best of all worlds, certainly not, but it looks like that's all we have for now (and what made pages 7-8 of this issue possible). While the major journals and a couple of the med-ed/CME web sites are doing a reasonable job of highlighting industry ties, professional associations, the ACTG, the FDA Antiviral Advisory Committee and some less reputable treatment information providers make it difficult if not impossible to know who's writing what for whom. TAGline welcomes comments, corrections, updated disclosure and other information at tagnyc@msn.com. †

Why the Famed \$800M Drug Is Really Closer to \$200M

The famed Tufts [†] number =	\$802 M
Back out imputed opportunity costs" =	\$403 M
Adjust for R&D tax breaks =	\$266 M [§]

[§]The \$266 million estimate applies to NMEs ("new molecular entities"), developed entirely in-house, only. Angell notes that since most newly licensed drugs entering the market these days are neither really new nor developed entirely in-house (i.e., they are often acquired after early promising testing at smaller R&D outfits), the real cost per drug is probably somewhere "well under \$100 million."

[†]Joseph DiMasi, Tufts Center for the Study of Drug Development, 11/30/2001

Pharmaceutical Industry Marketing + Med Ed Budget, 2001

Marketing	\$19.1 B
Free samples	\$10.5 B
Drug reps	5.5
DTC advertising	5.5
Medical journal ads	.4
Medical Education and Communication Companies ("MECC")	\$35.0 B
Total	\$54.1 B

Source: Robert Pear, "Drug Companies Increase Spending on Efforts to Lobby Congress and Governments," NYT, March 14, 2004. A1

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smoke it. Then I started smoking heroin, and became addicted without realizing it. I didn't have any money, I was feeling withdrawal symptoms, and my friend offered to share his heroin and inject me. Yes, it was scary the first time.

I got arrested at least twenty times. Most of the time, I did not have any drugs on me. The police would plant drugs on me and force me to confess, and beat me if I did not sign their document. I could not carry a needle around, because if the police arrested me the charge would be more serious.

I heard about the risk of getting HIV from sharing needles, but when you are craving heroin, you don't think about anything else. You just want to inject. I was in prison twice. The conditions were terrible and we had to stay in our cells for more than fifteen hours a day. For me, there is nothing worse than losing your rights and your freedom. I am not surprised that people use drugs and inject in prison, even if they never used or injected before. I believe that I got HIV in prison because I injected almost every day there.

Getting off drugs is not easy. Many times, I went into drug treatment just to please my family, get away from the police, or take a break because the amount of drugs I needed was getting expensive, not because I wanted to quit; and the attitudes of treatment staff only made me feel worse.

Other times, I really did want to quit. But can you imagine how it feels to leave a treatment program and go back home with nothing to do? How difficult it is to find a job and explain where you've been? My own family would watch my every move; I could see in their eyes they did not trust me. I was too embar-

rassed to see my friends, whose lives seemed so successful. It was so lonely. I felt I had nothing at those times. The only thing I could think of was to go back to using drugs.

Finally thirteen years ago I got off

Contaminated needles account for the largest share of new infections in Eastern Europe and Asia.

drugs. I knew I really needed help. I decided to go to a "TC," or "therapeutic community." This is how I found out how I had HIV. The test still is a requirement for entering the TC. There was no pre- or post-test counseling. In fact, my results were given to my sister—not to me.

Today, not much has changed. Drug users are still seen as morally weak and bad people. We face stigma and discrimination in society and in the health care setting. We experience constant police harassment and ineffective services. In Thailand, injecting drug users or "IDUs" are the only group whose 50% HIV prevalence has not changed in fifteen years. One third of all new HIV infections are IDU-related, and this number is increasing. Yet there has been no effective response from the government.

In a recent war on drugs in Thailand, over 2,500 people were killed extra-judicially in the first three months of the campaign. More than 50,000 people were arrested, hundreds of thousands were forced into military-run rehabilitation centers, and drug users were forced underground and away from services that were already difficult to access.

Last year, the Thai Drug Users'

Network developed a proposal for a peer-driven HIV prevention, care and support intervention for injectors, and submitted it to the Global Fund. We had to bypass the country coordinating mechanism and lobby with the help of international AIDS activists to get political support for our proposal. In October, we were awarded a 1.3 million dollar grant, but we still haven't received the money. Even though the Thai government says its current policy is to treat drug users as "patients," not "criminals," it is still illegal to be a drug user. We continue to be arrested and offered

the choice of prison or military-run rehabilitation centers. Is this harm reduction or harm production?

Every minute a person is infected with HIV by using a dirty needle. Globally, one in three of all new HIV infections outside of Africa is IDU-related. In fact, contaminated needles account for the largest share of new infections in Eastern Europe and Asia. The World Health Organization says drug users have an equal right to all levels of care, but in practice we are denied access to antiretroviral treatment, as well as basic prevention interventions like clean needles. Methadone is still illegal in many countries and should be included on the WHO Essential Drug List. There are many harm reduction interventions which have been proven to help IDUs stay free of HIV, including clean needles and methadone. We need these means of prevention in place *now!* And we need access to treatment *now!*

Drug users, like other politically, socially, or economically marginalized groups, are easily abused by the government and others, who exploit them for money or services. We often do not enjoy even the most basic human rights. In Thailand, this is true for sex workers, men who have sex with men,

migrant workers and undocumented citizens as well.

The world we live in today is not a world of sharing but of advantage-taking, profit-seeking, and competition to “get ahead.” It is a world motivated by greed and controlled by corporations, which do not recognize the value of a human being. While an elite few amass enormous wealth, basic needs are denied to many millions.

Today, many of our governments are run by these elite, who are more interested in protecting their personal investments than promoting public welfare. They invest public resources in projects whose profits go into the pockets of their friends instead of providing for the welfare of society. Governments privatize our public utilities, as well as our education and health care systems. Social welfare programs and other forms of assistance become issues of charity, not rights or entitlement. As a result, our public hospitals are overloaded and underfunded, severely compromising the availability and quality of treatment and care offered.

Of course, tackling AIDS isn't just about health care and antiretrovirals. Prevention, harm reduction, poverty reduction and decent living standards are all part of the process; but governments, like the United States, or international organizations, like the World Trade Organization (WTO), make the task much more difficult. Market-driven policies and the emphasis on “abstinence-only” have already proved to be harmful or, at best, totally useless. It is outrageous that today conservative groups, especially in the U.S., are advancing a moralistic ideology that contradicts scientific evidence about HIV prevention. Though condoms and clean needles are the most effective tool we have to prevent the transmission HIV,

programs that promote them are not funded, or are de-funded.

Evidence shows that widespread access to antiretrovirals leads to huge improvements in health and quality of life, with significant reductions in health care and other

Market-driven prevention policies and the emphasis on “abstinence only” have proved to be harmful at worst and totally useless at best.

costs, because of improved health and productivity among people living with HIV/AIDS and their families. The most painful experience I can think of, after living with HIV for thirteen years, is being poor and HIV-positive. Again and again, I watched many friends die in front of me, from terrible opportunistic infections, simply because they were poor and could not afford treatment. What kills us is not AIDS, but greed.

Multinational pharmaceutical companies inflate the prices of their drugs without thought for poor people. They use their wealth to influence U.S. and European government policy to ensure that intellectual property rights are weighed in their favor. Other governments say they are too worried about adherence and drug resistance to offer treatment, when the truth is they don't want to pay or suffer repercussions from their trading partners by breaking patents.

Four years ago, Thai people with HIV/AIDS asked the government to use a compulsory license for ddI, but the government was too afraid of trade and other sanctions from the U.S. Ultimately, we took Bristol Myers-Squibb to court and won the right to produce tablet-form ddI, locally. In the final judgment,

the Thai Court ruled that, because patents can lead to high prices and limit access to medicines, patients have the right to sue the patent holder. This was a very important battle that we won.

But the war is not over. Recently, the Thai government entered Free Trade Agreement negotiations with the United States. We know the U.S. unilaterally pushes for intellectual property protection that is stricter than what is agreed internationally. This means that Thailand, now producing generic antiretrovirals for most

who need them, will no longer be able to sustain this important program. We are demanding the Thai government refuse to trade away the health of its people by negotiating intellectual property protections for medicines.

The U.S. government and its policies affect the ability of people all over the world to enjoy their basic rights and needs. Many poor countries cannot provide basic services like health care because they have to pay back enormous debt to the U.S. and Western banks. While thousands die of AIDS everyday from lack of funds, there is unlimited funding for war. Billions of dollars are freely available for the killing and destruction in Iraq, while the Global Fund is out of money. This is because of the broken promises of rich donor countries that refuse to pay their fair share.

I have no simple solutions for achieving world peace, but I do know that the U.S. government, led by that criminal, George Bush, wages war and occupies countries like Iraq in the name of peace. The U.S. is too arrogant to listen to the United Nations, and the Thai government shows its loyalty to the U.S. by sending Thai troops to Iraq.

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Four years ago, at UN General Assembly Special Session (UNGASS) on HIV/AIDS, after activists demanded an urgent response to the global AIDS treatment crisis, Kofi Annan called on all the world's governments to develop what he described as a "war chest." This became the Global Fund. At the last international AIDS conference, the World Health Organization launched its "3 by 5" initiative; yet, today, six million people are still waiting for their drugs. AIDS doesn't wait and neither do we. Faced with the abuse of power and greed of corporations, we cannot wait for our governments to act.

Governments and corporations hate activists because we know what they are up to, and we are pulling the masks of fake concern from their face to reveal their true nature. But to me, activists are to be honored. Activists are my true friends. They stand by my side when I face discrimination and injustice. They have the courage to stand up to those in power who use their positions for their own benefit. They are the ones who can help provide a way forward to fight AIDS and injustice in this world.

"Access for all" is the theme of this conference and the dream of many

of us here. Yes, it's not easy to achieve in the world we live in today, but the world belongs to all of us to change.

Five years ago, doctors, nurses, and many other people told me and my friends that access to antiretrovirals was an impossible dream. Recently, Thailand announced that it would provide antiretrovirals to all who need it, starting with 50,000 people by the end of this year. Today, I urge all of us to dream of a day when our world will be filled with love, sharing and peace. And I believe that when we dream together, our dreams come true. †

The Irony of Bangkok **How To Get 6M Poor People On Antiretroviral Therapy—And 1M Rich People Off**

In a brief July editorial, "Freedom of Choice," UK-based AIDS Treatment Update editor Edwin Bernard captures the essence of the present day therapeutic conundrum. "It's ironic," he writes, "that whilst the main focus of this summer's XV International AIDS Conference in Bangkok was on finding ways to get everyone who needs therapy onto HAART, treatment interruption has become a hot topic in well-resourced countries, as concerns over resistance and side effects are increasingly recognised as issues in managing HIV disease."

Whereas at last summer's IAS conference in Paris, two key week on, week off (WOWO) intermittent treatment studies (the Dutch Staccato study and the NIH's own WOWO trial) led to disappointment, this year there has been renewed interest in the concept of *pulsed therapy* driven by CD4 cell count measures (cycling on and off ART according to pre-defined CD4 count thresholds), due in part to promising preliminary results from the Italian BASTA trial and publicity surrounding the ongoing SMART trial, which is currently enrolling study volunteers in 22 countries worldwide. There was even an admittedly symbolic renaissance of exploration into induction/maintenance approaches.

The BASTA study has patients go off therapy at a CD4 cell count of 800 and then back on at a threshold of 400. The stop/re-start threshold for SMART (www.smart-trial.org) are lower: off treatment once the CD4 cell count rises above 350; re-start if it falls below 250. Edwin's excellent overview of these two key studies can be found at <http://www.aidsmap.com>.

New or updated results from CD4-guided pulse therapy studies (and one intermittent rx protocol) presented at Bangkok include:

- *Ananworanich J, Siangphoe U, Cardiello P, et al.* A randomized trial of continuous, CD4-guided and one week on—one week off HAART in 74 patients with chronic HIV infection: week 108 results. Abstract WeOrB1283.
- *Cohen CJ, Morris A, Bazner S, et al.* The FOTO Study: A pilot study of short-cycle treatment interruption, taking antiretroviral medications for Five days On, Two days Off (FOTO), for those with viral load suppression. Abstract TuPeB4575.
- *Mussini C, Cozzi-Lepri A, Borghi V, et al.* A multicentre study on CD4 count-guided treatment interruptions. Abstract TuPeB4569.
- *Ruiz L, Gomez G, Domingo P, et al.* A multicenter randomized controlled clinical trial of continuous vs. intermittent HAART guided by CD4+ T cell counts and plasma HIV RNA levels: two-year follow-up. Abstract TuPeB4567

Intriguing results from studies exploring a second therapy-sparing treatment approach, "induction/maintenance", include:

- *Arribas JR, Pulido F, Lorenzo A, et al.* Simplification to lopinavir/r single-drug HAART: 24 weeks results of a randomized, controlled, open label, pilot clinical trial (OK Study). Abstract TuPeB4486.
- *Girard PM, Cabie A, Michelet C, et al.* EFV/TDF vs EFV/3TC/TDF as maintenance regimen in virologically controlled patients under HAART: a 6-month analysis of the COOL Trial. Abstract TuPeB4493.
- *Markowitz M, Hill-Zabala C, Lang J, et al.* Maintenance with Trizivir (TZV) or TZV + efavirenz (EFV) for 48 weeks following a 48-week induction with TZV + EFV in antiretroviral-naïve HIV-1 infected subjects. Abstract LbOrB14.
- *Ruane P, Luber A, Gaultier C, et al.* Maintenance therapy using lopinavir/ritonavir (LPV/r) alone with well-controlled HIV Infection. Abstract TuPeB4577.
- *van Raalte R, Heere B, Regez R, et al.* Induction-maintenance strategy re-evaluated: initial boosted-PI in combination with triple NRTI, followed by triple NRTI maintenance. Abstract TuPeB4597.

Camel's Nose Under the Tent
Who Evaluates and Licenses the Drugs You're Taking?

cf. M Angell, "The Hard Sell... Lures, Bribes, and Kickbacks"

1. Who approves your drugs?

FDA's Antiviral Advisory Committee (AVAC) membership and ties to industry:

Roy M. ("Trip") Gulick, MD, MPH, Chair

Consultancy fees from two pharma companies (not identified) of less than \$20,000 a year; and research funding from two pharma companies (not identified) of less than \$20,000 a year (per 2004 AVAC transcript). Consultancy fees from: Bristol-Myers Squibb, GlaxoSmithKline, Triangle, Trimeris; Speaking fees from: Abbott, Agouron, GlaxoSmithKline, Pharmacia-Upjohn (now part of Pfizer), Triangle.†

Tara P. Turner, Pharm. D., Executive Secretary

"Nothing to report"

Victor G. DeGruttola, Sc.D.

Pharmaceutical stock ownership totaling less than \$5,000

Janet A. Englund, MD

"Nothing to report"

Courtney V. Fletcher, Pharm. D. (Consumer Rep)

Pharmaceutical stock ownership totaling less than \$50,000

Princy N. Kumar, MD

Pharmaceutical stock ownership (including but not limited to Schering-Plough) totaling less than \$30,000; advisory fees from Schering§

Wm. Christopher Mathews, MD

"Nothing to report"

Kenneth E. Sherman, MD, Ph.D.

Pharmaceutical stock ownership totaling less than \$25,000

Lauren V. Wood, MD

"Nothing to report"

Eugene Sun, MD (nonvoting industry representative)

Employed by Abbott Laboratories; not required to make disclosures

Joel Morganroth, MD (nonvoting consultant)

Not required to make disclosures

Douglas G. Fish, MD (voting consultant)

"Nothing to report"

Peter R. Kowey, MD

Consultancy and speaking fees from pharma companies totaling less than \$100,000 a year.

D. Roger Illingworth, MD, Ph.D.

Consultancy and speaking fees from two pharma companies totaling less than \$60,000 a year.

Rory P. Rimmel, Ph.D.

"Nothing to report"

Thomas R. Tephly, MD, Ph.D.

"Nothing to report"

Ronald G. Washburn, MD

Pharmaceutical stock ownership totaling less than \$150,000

Matthew Sharp (voting patient representative)

"Nothing to report"

Aggregate total disclosed:

Less than \$400,000 per year

Angell: "The FDA's advisory committees should not include experts with financial ties to industry. The notion that they are somehow indispensable is not credible. No one is indispensable. The truth is that experts who have deals with drug companies are being co-opted, just as the FDA is co-opted by user fees." TTATDC, p 244

Source: DHHS/FDA/CDER transcript, Antiviral Drugs Advisory Committee (AVAC) Meeting, Tuesday, May 13, 2003. "NDA 21-567 and 21-568, Reyataz™ (atazanavir sulfate) capsules and powder for oral use, Bristol-Myers Squibb Company, proposed for the treatment of HIV infection in combination with other antiretroviral agents"; †per 2000 disclosure; § (per 11/02 documents)

Dancing with the Devil

Who Tests (and Reports on) the Drugs You're Taking—and Formulates Your Treatment?

cf. M Angell, "The Hard Sell... Lures, Bribes, and Kickbacks"

2. Who (at the NIH) tests your drugs?

ACTG HIV Research Agenda Committee (RAC) membership and ties to industry:

Joseph J. Eron, Jr., M.D.

Consulting arrangements with GlaxoSmithKline, Merck, Triangle, Trimeris. Research grants: GlaxoSmithKline, Merck, Abbott, Agouron, Triangle, and Trimeris.

Roy (Trip) Gulick, M.D., M.P.H.

Consultancy fees from two pharma companies (not identified) of less than \$20,000 a year; and research funding from two pharma companies (not identified) of less than \$20,000 a year.[#] Consultancy fees from: Bristol-Myers Squibb, GlaxoSmithKline, Triangle, Trimeris; Speakers bureau services for: Abbott, Agouron, GSK, Pharmacia-Upjohn (now part of Pfizer), Triangle.

Ann C. Collier, M.D.

Consulting arrangements with Merck. Research grants: Agouron, Merck, Hoffmann-LaRoche, Glaxo-Wellcome, and Anor Med.

Eric S Daar, M.D.

Consulting arrangements with Abbott, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Serono, ViroLogics. Speaking honoraria from: Abbott, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Roche, Merck, Serono, ViroLogics, Ortho. Research grants: Abbott, Bayer, GlaxoSmithKline, Gilead, Roche, Merck, ViroLogics, Serono.[†]

Margaret A. Fischl, M.D.

Consultancy arrangements with and grant support (not broken out in disclosure) from: Abbott, Agouron, Bristol-Myers Squibb, DuPont, GlaxoSmithKline, Triangle.[§]

Richard Haubrich, M.D.

Speakers bureau member for: Agouron, GlaxoSmithKline, Trimeris, ViroLogics; Grant support from same.[†]

Victoria A. Johnson, M.D.

(Nothing found)

John W. Mellors, M.D.

Consultancy fees from: Agouron, Bristol-Myers Squibb, DuPont (now part of BMS), GlaxoSmithKline, Gilead, Merck, Novirio, Pharmasett, Triangle, Virco, Visible Genetics^{††}; Grant support: BMS, Chiron, DuPont (now part of Bristol), GlaxoSmithKline, Merck.

Andrew R. Zolopa, M.D.

Consulting arrangements with Abbott, Bristol-Myers Squibb, and Merck. Research grants: Abbott, Bristol-Myers Squibb, and DuPont.[†]

Angell: "You need to know that your doctor's decisions are based solely on what is best for you. And doctors need to be weaned from their dependence on drug company largesse." *TTATDC, p 262*

Angell: "It is impossible to know to what extent these financial deals influence judgments about... research priorities or the interpretation of results, but they certainly are cause for concern." *TTATDC, p 105*

3. Who sets your treatment guidelines?

International AIDS Society (IAS) guidelines panel membership and ties[§] to industry:

(U.S. based members only. Pharma ties of the six extra-U.S. panel members (Yeni, Cooper, Gatell, Gazzard, Montaner, Vella) are extensive.)

Scott Hammer

Consultancy fees and grants (not broken out in disclosure): Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Roche-Trimeris, Shionogi, Shire BioChem, Tibotec-Virco, Triangle.

Charles Carpenter

"None to report"

Margaret Fischl

Advisory fees and grant support (not broken out in disclosure) from: Abbott, Agouron/Pfizer, Bristol-Myers Squibb, DuPont, GlaxoSmithKline, Triangle.

Martin Hirsch

Consultancy and lecture fees and grant support from: Bristol-Myers Squibb, GlaxoSmithKline, Merck, Schering-Plough, Takeda, Trimeris.

David Katzenstein

Stock holdings, advisory fees, speaking honoraria and grant support (not broken out in disclosure) from: Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, ViroLogics, Visible Genetics, patent US 5,968,730 on PCR assay (October 15, 1999).

Doug Richman

Consultancy arrangements with Abbott, Bristol-Myers Squibb, Chiron, Gilead, GlaxoSmithKline, Merck, Pfizer, Roche, Takeda, Triangle, ViroLogics.

Mike Saag

Grant support from or served as a consultant (not broken out in disclosure) or on the speakers bureau for Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Hoffmann-La Roche, Ortho Biotech/JNJ, Pfizer/ Agouron, Pharmacia & Upjohn, Schering-Plough, Shire, TherapyEdge, Tibotec/Virco, Triangle, Trimeris, and ViroLogics.

Mauro Schechter

Consultancy fees, speaking honoraria and grant support (not broken out in disclosure) from: Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Roche.

Melanie Thompson

Consultancy and advisory fees, lecture sponsorship, speaking honoraria and grant support (not broken out in disclosure) from: Abbott, Agouron, Agouron/Pfizer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiron, DuPont, Gilead, GlaxoSmithKline, Merck, Oxo-Chemie, Roche, Serono, Triangle, Trimeris, ViroLogics.

Chip Schooley

Stock holdings (options), consultancy and lecture fees, honoraria and grant support (not broken out in disclosure) from: Agouron, AnorMed, Bristol-Myers Squibb, Merck, Mojave, Pan Pacific Pharmaceuticals, Hoffmann-La Roche, Tanox Biosystems, Triangle, Vertex, ViroLogics.

Paul Volberding

Consultancy fees and honoraria from: Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck.

Angell: "Increasingly, panel members and med 'educators' are required to disclose their financial ties. And that disclosure is supposed to make it acceptable that they have them." *TTATDC, p140*

4. Who provides your with up-to-date treatment information?

Patient (and clinician CME/"med-ed") education outfits, magazines, websites—and ties to industry: (*internet only*)

Medscape.com, TheBody.com, clinicaloptions.com/imedoptions.com, hivandhepatitis.com, Poz, PRN (Physicians Research Network), AAHIVM (Am. Academy of HIV Medicine), aidsmap.com

[†] Medscape disclosures, 2001; [§] JAMA required disclosures from IAS guidelines panels, 2004 (IAS itself does not make this information available); [#] FDA AVAC transcript (see source reference on preceding page); ^{††} per JAMA 1999

**Estrategia de Apoyo a los
Tratamientos en el
Segundo Taller Anual
TB/VIH Internacional
Organizado por TAG**

Activistas de 31 países

En vistas del éxito obtenido en el Primer Taller Internacional TB/VIH de Educación Comunitaria y Movilización, llevado a cabo junto con la 33ª Conferencia organizada por la Unión Internacional contra la Tuberculosis y Enfermedad Pulmonar (IUALTD) acerca de la Salud Pulmonar, que se realizó en Montreal en el 2003, el Segundo Taller Internacional TB/VIH de Educación Comunitaria y Movilización se propuso los siguientes objetivos:

1. Educar a los representantes de la comunidad VIH acerca de los diferentes aspectos de las investigaciones, prevención, tratamiento y política referidas a la coinfección TB/VIH.
2. Otorgar poder a los representantes de la comunidad VIH para movilizar y diseminar información acerca de la coinfección TB/VIH en sus comunidades locales.
3. Dotar a los representantes de la comunidad VIH de las habilidades necesarias para ayudar a que sus comunidades comprendan, participen y provean información en las investigaciones y ensayos clínicos.
4. Brindar la oportunidad de que los represen-

tantes internacionales de la comunidad VIH desarrollen una relación de trabajo con WHO, la Asociación Stop TB, el Fondo Global y otros interesados, para representar de manera más efectiva a las comunidades afectadas en temas referidos a prevención, investigación, tratamiento y programas de atención enfocados en la coinfección TB/VIH.

5. Brindar la oportunidad de que los representantes internacionales de la comunidad VIH desarrollen una relación de trabajo con salud pública nacional y regional y TB y los oficiales de los programas de VIH/SIDA, a fin de que puedan trabajar de manera conjunta en la implementación de futuras iniciativas concernientes a la temática TB/VIH.
6. Brindar la oportunidad de que los representantes internacionales de la comunidad VIH desarrollen planes y estrategias para movilizar a sus comunidades, a sus legisladores y a sus recursos para mejorar la lucha contra TB/VIH a nivel nacional y regional y para facilitar su participación en el diálogo global acerca de dichas políticas.

El 2do. taller incorporó varios cambios a fin de atender las necesidades identificadas por los participantes durante el 1er. taller. Asistieron 50 participantes. El taller tuvo una duración de dos días y medio. Hubo más oportunidades para la interacción de pequeños gru-

pos y sesiones estratégicas más prolongadas. Como en el 2002, los participantes del 2do. taller asistieron a las conferencias acerca de la coinfección TB/VIH organizadas por la IUATLD, se reunieron con oficiales del programa de TB y trabajaron extensivamente en red en la reunión de la Unión para establecer relaciones más fuertes con salud pública nacional y regional, oficiales de los programas de TB y VIH/SIDA, la Organización Mundial de la Salud (WHO—World Health Organization), la Asociación Stop TB, el Fondo Global para la lucha contra el SIDA, la tuberculosis y la malaria (GFATM) y otros para representar de manera más efectiva a las comunidades afectadas.

Más de un millón de personas en el mundo muere de tuberculosis cada año, según la Organización Mundial de la Salud. La tuberculosis, una enfermedad 100% curable, hoy en día causa silenciosamente más muertes que nunca en la historia de la humanidad.

“TB es el mayor asesino de las Personas que Viven con VIH/SIDA (People Living with HIV/AIDS—PLWHA). Lo sé porque ví morir a mis hermanos. Yo también estaría muerto. Hoy estoy vivo porque tuve acceso a tiempo a un tratamiento para la TB”, dijo Winstone Zulu de la Red de Personas que viven con VIH en Zambia, durante la conferencia en París de la IUATLD del 2003. “Nunca pensé que la tuberculosis fuera un problema hasta que perdí a cuatro hermanos a causa de esta enfermedad en un lapso de tres años”, dijo.

“Muchas personas desconocen que tienen tuberculosis hasta que es demasiado tarde”, sostu-

vo Nomfundo Dubula, de la Campaña de Acción de Tratamiento de Sudáfrica. “Padecí tuberculosis también y fue difícil continuar con la medicación”, dijo ella. “La detección temprana y el tratamiento rápido salvaron mi vida. No lo hubiera logrado sin ayuda. El temor a tener que iniciar nuevamente el tratamiento si no completaba mis dosis fue lo que me hizo seguir adelante”.

“La dificultad en el diagnóstico de los casos de TB nos ha robado la vida de muchas

Personas que Viven con VIH/SIDA en Brasil”, dijo Ezio Santos-Filho, del Grupo Por la VIDDA, un grupo de VIH-positivos en Río de Janeiro.

“El activismo por el SIDA no puede sostenerse sin el activismo por la TB”, sostuvo Fabio Scano, del programa Stop TB, de la WHO. “La movilización social y la participación comunitaria que impulsó la respuesta al problema del VIH/SIDA es necesaria para luchar contra la TB”.

Una mirada más profunda a la epidemia mundial de TB no pudo haber sido más forzada, en tanto los científicos e interesados se reunieron durante cuatro días en el otoño del 2003 para examinar las tendencias actuales, los avances científicos y los progresos realizados en el control de la epidemia global.

Los científicos se reunieron bajo la égida de la IUATLD. Mientras que los investigadores intercambiaban información durante la conferencia, los involucrados en tratamientos participaron del Taller de Educación y Movilización Comunitaria para la coinfección TB/VIH organizado por el

Treatment Action Group (TAG). El taller fue diseñado para estimular la discusión acerca de los principales problemas que alimentan la co-epidemia TB/VIH y las estrategias para abordarlos.

El activismo por el sida no puede sostenerse sin el activismo por la TB.

Para muchos de los más de 60 activistas en tratamiento de 31 países que asistieron al taller, las discusiones en los diversos grupos actuaron como un elemento para abrir los ojos ante los estragos que, sin ser dicho, la TB está causando en muchas comunidades, su relación intrínseca con el VIH y la necesidad de adoptar estrategias proactivas para limitar esta “epidemia silenciosa”.

Se identificaron varios factores que alimentan esta situación, tales como la creciente incidencia de nuevos infectados con VIH, las empobrecidas instalaciones para realizar diagnósticos, la baja detección de nuevas infecciones de TB y la falta de profesionales bien entrenados para el cuidado de la salud. Otros factores incluyen el “agotamiento cerebral”, los fondos insuficientes destinados a los programas nacionales de TB, la falta de liderazgo político, la insuficiente provisión de drogas para los centros de tratamiento de TB y la incidencia de la resistencia multi-droga.

Los informes de situación presentados sobre el estado de los programas de TB en muchos

países, incluyendo Nigeria, Ucrania, Sudáfrica, Brasil, Zambia, Tailandia, Kenia y Nigeria revelaron que, a pesar de sus más de tres décadas de existencia, los programas nacionales de TB siguen siendo groseramente sub-fondeados y requieren de un compromiso político más fuerte para frenar la marea que constituye esta epidemia.

Pareciera que los programas de TB tienen casi nada, en comparación con los programas nacionales de VIH, que gozan de

abultados presupuestos, el soporte de donaciones externas, alto grado de voluntad política y compromiso, la involucración de la población civil y de la comunidad, el apoyo de grupos de pares establecidos y recursos humanos entrenado.

El Dr. Gani Alabi, del staff de WHO que trabaja en TB en el Sudoeste de Nigeria, dijo, “Nigeria posee un comité de VIH/SIDA fuerte, encabezado por el Presidente, un comité multisectorial conformado por representantes de muchos sectores, incluyendo grupos provenientes de la sociedad civil que trabaja en VIH/SIDA. Estas intervenciones reciben muchos fondos y cuentan con el personal que necesitan. Desgraciadamente, los programas de control de TB en el país no cuentan con este tipo de apoyo”.

Continuó diciendo: “Aunque existe una política de tratamiento de TB gratuito, muchos de los centros de tratamiento de TB no cuenta con las drogas necesarias para sus clientes cuando ellos las necesitan. La WHO planea

— sigue en la próxima página —

— viene de la página anterior —

comenzar a integrar los programas de TB/VIH en seis estados del país, seleccionados para tal fin, pero se necesita compromiso político y financiero para que ésto se haga realidad”.

Karyn Kaplan, del Treatment Action Group de Tailandia (TTAG) también señaló que mientras que el Fondo Global para la lucha contra el VIH / SIDA, Tuberculosis y Malaria presenta una gran oportunidad para financiar propuestas que expandan las intervenciones en TB, ha habido escaso o ningún compromiso significativo de PLWHA (Personas Viviendo con HIV/SIDA) o de aquellos afectados por la TB en los Mecanismos de Coordinación de Países en aquellos países que deberían estar peleando por recibir fondos.

Al finalizar las deliberaciones, los participantes recomendaron la integración de los programas ya existentes de VIH y TB y la necesidad de movilizar el apoyo comunitario para la Directly Observed Treatment Strategy (DOTS) en la reducción de la expansión de TB.

Los activistas también propusieron varias otras actividades de seguimiento a nivel país para apoyar la actividad de DOTS. En el primer lugar de la lista de recomendaciones se encuentra la necesidad de organizar talleres para promover la capacidad de comprender el tratamiento y educación comunitaria acerca de los signos y síntomas de la TB, la adherencia y cumplimiento de las drogas. También acordaron reforzar las coaliciones

nacionales de TB y movilizarse para lograr un mayor compromiso político y financiero por parte de los gobiernos, agencias de donación y grupos civiles para los programas de control de la TB.

Los programas de TB tienen casi nada en comparación con los programas nacionales de VIH, que gozan de abultados presupuestos.

¿Cómo puede el activismo sida contribuir al control de la TB?

Los movimientos activistas SIDA han desarrollado habilidades y estrategias que pueden adaptarse para ser utilizados en campañas contra TB y TB/VIH. Una de las principales estrategias es incrementar el gasto nacional en investigación, prevención, tratamiento y cuidado. Lograr mayores fondos para los Institutos Nacionales de Salud ha sido uno de los principales objetivos de TAG.

El presupuesto para la investigación de TB es bastante reducido en comparación con la carga que implica esta enfermedad. Mientras que el NIH gasta \$ 2.700 millones cada año en investigación sobre VIH/SIDA, gasta apenas algo más de \$200 millones en investigaciones sobre TB. Se necesitan más investigaciones en regímenes más cortos de TB, mejores drogas, diagnósticos en el punto de uso, interacción entre drogas antiretrovirales y drogas TB. Drogas para prevenir y tratar las infecciones oportunistas, tales como cotrimoxazol e isoniazi-

da, también son componentes críticos del cuidado de TB/VIH.

En los últimos 100 años ha habido diferentes fases en el apoyo a la TB, desde los movimientos sanitarios hasta DOTS. Hoy se registra un impulso para ligarlo a la fortaleza de los movimientos internacionales de acceso al tratamiento de SIDA, pero la involucración de PWA (People With Aids) en todos los niveles como estrategia principal, es difícil de replicar con TB, dado que, a diferencia del VIH, no es una condición para toda la vida.

En los EE.UU., el precio anual del AZT (\$10.000) desde su aprobación en 1987 generó una indignación de tal magnitud que contribuyó a la fundación de ACT UP. Las estrategias “Involucrados/No Involucrados” pueden ser útiles y complementarias: los activistas identifican los problemas y se reúnen con los legisladores, al mismo tiempo que generan presión a través de los medios y la movilización social.

El precio de las drogas sigue siendo un problema, aunque la presión continua ha hecho bajar los precios de las terapias antiretrovirales genéricas. No obstante, en la mayoría de los escenarios de los países menos desarrollados, las terapias antiretrovirales necesitarán ser gratuitas. Los países más ricos necesitarán proveer los recursos para que esto suceda. Aún si los programas de terapias antiretrovirales costaran \$500 por persona por año, para tres millones de personas ésto significaría sólo un gasto de \$1.500 millones, que es el costo semanal de la ocupación norteamericana a Iraq. †

— viene de la primera página —

VII. Algunos statins han sido implicadas en mayor medida que otras en su potencial para interactuar con terapéuticas antiretrovirales.

Es extremadamente importante implementar modificaciones en el estilo de vida, tales como dejar de fumar. Los ajustes dietarios también constituyen un modo eficiente para bajar los niveles de colesterol y pueden provocar reducciones de hasta 10-20%. Para reducir los niveles de colesterol de un modo aún más significativo, podría ser necesaria la utilización de statin a fin de disminuir los niveles de colesterol de LDL.

Hydrochlorothiazide (una droga diurética y antihipertensiva, comercializada bajo el nombre de *Hydrodiuril*) y atorvastatin deberían controlar la presión arterial y el colesterol LDL, pero frecuentemente aparecen mialgias y debilidad muscular luego de un corto tiempo de administradas. Se recomienda monitorear los valores serológicos de LFT y CPK para observar si se incrementan—ya que statin posee el potencial de causar toxicidad muscular. En tal caso, se recomendaría discontinuar el statin. Cambiar a fenofibrate (*TriCor*) puede reducir los valores del VLDL (lipoproteínas de muy baja densidad), pero no es tan efectivo para reducir los incrementos en los niveles de LDL-C (lipoproteínas de colesterol de baja densidad)

Algunos puntos importantes para tener en mente:

- No todos los statins son iguales—tanto en términos de eficacia o en su propensión a la interacción con otras drogas
- Todos los statins poseen la capacidad de ser severamente tóxicos, incluyendo

algo llamado rhabdmiolisis (básicamente, la rotura de fibras musculares que da por resultado la liberación en sangre de los contenidos de la fibra muscular. Ello puede someter los riñones a un nivel de stress que

Todos los statins poseen la capacidad de ser severamente tóxicos.

cause daño renal) y disfunciones hepáticas, que dependen de la dosis.

- Comprender el metabolismo de las drogas statin facilitará la predicción de posibles interacciones de droga-a-droga.

Estructura de los Statins

Simvastatin y lovastatin son prodrogas de lactona, que deben ser convertidas a la forma de ácido hidróxido para lograr ser más lipofílicas y activas. Rosuvastatin (*Crestor*) es el más nuevo en su clase (y es objeto de mucha atención por parte de los medios con relación al riesgo de toxicidad renal). Los statins son metabolizados por CYP450.

Impacto de los inhibidores e inductores CYP450 sobre el metabolismo de los Statins

Simvastatin es significativamente metabolizado en ácido simvastatin por la vía del CYP3A. La inhibición de CYP3A4, como sucede con muchos de los inhibidores de proteasa de VIH, puede conducir a aumentos poco significativos de los niveles del ácido simvastatin—y a toxicidades indeseadas. Un estudio que investiga el impacto de ritonavir en el metabolismo de las dro-

gas statin, demostró una acumulación de los niveles de ácido simvastatin notablemente alta, con incrementos que rondaron el 3,000%

Pravastatin, por contraste, es metabolizado de manera diferente e involucra varias vías de oxidación a través del sistema CYP450—pero, significativamente, no con CYP3A. Entonces, los niveles de pravastatin en sangre se reducen (alrededor de un 50%) cuando se lo coadministra con ritonavir.

Los dos metabolitos activos de atorvastatin son generados por el CYP3A, por lo que la inhibición del CYP3A4 llevará nuevamente a incrementar los niveles de atorvastatin en sangre (tal como sucede con simvastatin) Aquí, la diferencia clave radica en que los niveles en sangre del metabolito activo disminuyen cuando el sistema CYP3A es inhibido. En tal caso, el incremento total en el nivel de atorvastatin activo no es tan grande: el incremento es alrededor del doble con ritonavir.

Con nelfinavir se observa un efecto similar al visto con ritonavir: se incrementan los niveles de atorvastatin y los de simvastatin lo hacen significativamente. Información con lopinavir/r (*Kaletra*) también muestra incrementos en los niveles de atorvastatin—de hasta 5 veces. (Aunque en este estudio se examinaron únicamente los niveles de atorvastatin no modificados, sin que se examinara el nivel activo total de atorvastatin. *Kaletra* no mostró ningún cambio significativo con pravastatin)

Otros estudios han demostrado que la exposición a pravastatin se reduce en un 50% con el uso de ritonavir y saquinavir, en un 40% con efavirenz y en un 50% con nelfinavir. Efavirenz ha sido probado

— sigue en la próxima página —

HAART Continuo y la Ley de Rendimientos Decrecientes

Investigadores Franceses Cuestionan Los Beneficios del Tratamiento Antiretroviral de Por Vida

“El efecto de una terapia antiretroviral altamente activa durante 5 años”

Jean-Pierre Viard y colaboradores (Service d'Immunologie Clinique, Centre Hospitalier Universitaire Necker-Enfants Malades, París)

[extractos]

Se hace cada vez más difícil imaginar prescripciones de tratamientos anti VIH para toda la vida, dados los efectos descritos a largo plazo, tales como lipodistrofia (encontrado en cerca el 60% de los pacientes), desórdenes metabólicos, un posible incremento del riesgo cardiovascular, toxicidad mitocondrial y una calidad de vida alterada. En otras palabras, el inconveniente de un tratamiento a muy largo plazo puede tener un mayor peso que los beneficios de mantener alto el recuento de células CD4, considerando que los tratamientos que se mantienen por más de dos a cuatro años no resultarán en reducciones más significativas de la carga ADN del VIH-1. Para aquellos pacientes con altos valores de células CD4 (Ej: >400 células/mL) luego de este período [>2-4 años] en HAART, sería razonable considerar suspender la terapia cuando el nivel de ADN de VIH-1 alcanza su piso más bajo y esperar a que el paciente vuelva a alcanzar el criterio de iniciación de tratamiento?

El presente estudio, aunque limitado en sus conclusiones debido al reducido número de pacientes, enfatiza la tendencia a nivelar, con el tiempo, de los efectos del HAART. Mantener la terapia por más de tres años es necesario para evitar que se vuelvan a colmar los compartimentos de células que producen el virus activamente, pero es poco probable que la prolongación del tratamiento provea ningún beneficio adicional en términos de reducción del reservorio viral.

[Entre los pacientes que participaron de este estudio] se registró un incremento muy leve de las células CD4 luego de 18 meses de tratamiento. Más interesante aún, el incremento absoluto del recuento de células CD4 no fue diferente entre los pacientes que comenzaron con un valores por debajo o por encima del valor medio de la población, y no se registró ningún beneficio importante a largo plazo en ninguno de los grupos. Hacia el mes 30, la mayoría de los pacientes habían alcanzado un recuento de células CD4 constante de >400 células/mL, y casi todos aquellos que iniciaron el estudio con un recuento de células CD4 por encima de la media (135 células/mL) alcanzaron ese nivel hacia fines del seguimiento. El beneficio inmunológico de mantener el HAART parece discutible en el caso de los pacientes que alcanzaron dichos niveles en los recuentos de células CD4, habiendo llegado a un grado razonable de seguridad tanto de protección ante infecciones oportunistas como para considerar la interrupción del tratamiento.

En síntesis, los datos que aquí se presentan muestran que el ADN VIH-1 parece no estar influenciado por el HAART luego del tercer año y confirman que la recuperación en el recuento de células CD4 es menos evidente luego de 18 meses de tratamiento. En base a estas observaciones, cuestionamos los beneficios de un tratamiento de por vida para la infección por VIH.

Fuente: Jean-Pierre Viard y colaboradores: “Efecto de terapias antiretrovirales altamente activas durante 5 años”. *AIDS* 2004;18:45-49.

— viene de la primera página —

como un potente inductor del metabolismo del simvastatin, produciendo reducciones de un 60% en la exposición y de un 30% en la de atorvastatin. Reducciones significativas en los niveles de simvastatin, atorvastatin y pravastatin hacen más lento el descenso en los niveles del colesterol LDL en presencia de efavirenz.

Un simple análisis de los datos disponibles sobre los statins sugeriría que pravastatin y fluvastatin son seguros para ser utilizados con los inhibidores CYP450 3A4, aunque podría haber más datos disponibles acerca de fluvastatin. La

eficacia de pravastatin podría estar comprometida de alguna manera, en tanto que su metabolismo es inducido. De todos modos, atorvastatin debería ser utilizado con precaución, ya que la interacción droga-a-droga con antiretrovirales utilizados habitualmente podrían dar como resultado niveles peligrosamente altos de atorvastatin en combinación con inhibidores de la proteasa—y niveles inútilmente bajos al combinarse con efavirenz (y muy probablemente también con nevirapine, aunque es difícil conseguir datos al respecto).

En tanto que los niveles de droga en simvastatin y lovastatin se ven

severamente afectados por los inhibidores del sistema CYP3A4 (Ej.: inhibidores de la proteasa), estos statins no deberían ser coadministrados con los PIs.

Virtualmente no existen datos acerca de rosuvastatin, por lo que el uso de esta droga (*Crestor*) concomitante con HAART debería ser evitada, al menos por ahora. Existen preocupaciones inquietantes, sobre todo, acerca de daño muscular (rabdomiolisis) y su efecto sobre los riñones.

Statins y nevirapine

Actualmente no hay datos acerca de la interacción para los statins y nevi-

rapine. Hasta que estos datos estén disponibles, se sospecha que los efectos de la interacción serán similares a los producidos con efavirenz.

Tenofovir y otros NRTIs

Tenofovir sufre un complejo proceso metabólico que puede llegar a registrar significantes variaciones en el nivel de droga entre pacientes y, por lo tanto, trae consigo el riesgo de efectos adversos y respuestas antivirales. Se ha probado también que tenofovir incrementa las concentraciones de ddI en plasma, aunque el mecanismo de esta interacción no está aún esclarecido.

La forma activa de drogas nucleótidas análogas como el AZT, ddI, 3TC y análogos nucleótidos, tales como tenofovir, es el derivado fosforilado producido dentro de las células anfitrionas. Estos “anabolitos” permanecen dentro de la célula y allí son desfosforiladas. Lo que es más importante, el nivel de desfosforilización dentro de la célula puede diferir del nivel de desaparición (media-vida o $t_{1/2}$) del nucleótido que circula en el plasma.

La media-vida del tenofovir (circulante en plasma) es de aproximadamente 17 horas, mientras que el del anabolito desfosforilado puede ser de 50 horas –un PK más que adecuado para soportar su dosis de una vez al día. La fosforilización intracelular (de Tenofovir, pero también de todos los análogos nucleótidos) es difícil de medir. Si el anabolito desfosforilado constituye la medida importante, estaríamos dando sobredosis, por ejemplo, de Tenofovir cuando lo prescribimos una vez al día? Alguien ha investigado esto?

Nelfinavir y el monitoreo terapéutico de droga durante el embarazo

La utilización de drogas antiretrovirales durante el embarazo se com-

plica debido a factores tales como los cambios hormonales y metabólicos, así como también por la necesidad de asegurar a la madre y al feto. El uso del monitoreo terapéutico de droga (TDM) puede constituir una guía para los clínicos en el manejo de pacientes que

Simvastatin y lovastatin no deberían ser coadministrados con los PIs.

tienen niveles de droga por debajo o por encima del nivel óptimo.

Ejemplo: Una mujer embarazada inicialmente muestra una buena respuesta al HAART, a pesar de los bajos niveles de nelfinavir en plasma, pero un día su carga viral indetectable hace un salto. Los niveles de nelfinavir sean probablemente relevantes en este punto—se deberá incrementar la frecuencia de los monitoreos de la carga viral. Aumentar la dosis de nelfinavir puede llegar a ayudar a elevar los niveles de nelfinavir en sangre. Lo más apropiado sería hacer ambas cosas (repetir las cargas virales e incrementar la dosis)

Los niveles en plasma de nelfinavir pueden mantenerse bajos durante el embarazo. No se conoce si estos niveles bajos están asociados a respuestas antivirales por debajo de lo óptimo. Con nelfinavir, un régimen de TID (Tres veces al día) podría dar como resultado niveles de droga más confiables (aunque un estudio anterior sobre ACTG encontró que éste no es el caso) Serían de utilidad los futuros estudios farmacocinéticos sobre el uso de nelfinavir en mujeres embarazadas?

Algunos clínicos recomendarían incrementar la frecuencia de los

monitoreos de las cargas virales y realizar el monitoreo terapéutico de droga tan pronto como fuera posible. El monitoreo terapéutico de droga debería realizarse dos semanas después de iniciado el tratamiento y la interpretación de sus resultados debería ser utilizada para ajustarlo (junto con la respuesta virológica)

Resistencia y PK

El cuidado de pacientes que han tenido experiencias anteriores con múltiples agentes antiretrovirales y una limitada cantidad de opciones para cambiar, representan un desafío. Las opciones ter-

apéuticas pueden ser guiadas comprendiendo las mutaciones significativas que hacen a la resistencia a las drogas y el impacto de cambios acumulativos en la mutación viral.

Es poco probable que algún cambio de NRTI tenga mucho efecto en presencia de un número elevado de NAMs (mutaciones de análogos nucleótidos) más el M184V. Basándose en la opinión de los expertos y en la reciente debacle del GSK 30009 (abacavir + 3TC+ tenofovir es una prohibición!), con cuatro o más TAMs (mutaciones de análogos de timidina), el impacto de nuevos NRTIs es escaso. La coadministración de tenofovir y ddI produce un incremento en las concentraciones de ddI en plasma, y tenofovir + lopinavir/r incrementa los niveles de tenofovir.

La habilidad de los inhibidores de la proteasa para inhibir el virus con mutaciones resistentes acumuladas es un fenómeno relativo. Los virus pueden no ser completamente susceptibles, pero pueden seguir manteniendo cierto grado de actividad. Necesitamos comprender el impacto de la resistencia, así como combinar lo que pudieran ser drogas parcialmente activas en un régimen que confiera la mayor actividad acumulativa. Integrando las intervenciones

— sigue en la última página —

farmacológicas y virológicas podemos mejorar la actividad del inhibidor de la proteasa y mejorar los resultados terapéuticos.

Los principios farmacológicos se basan en la relación riesgo/beneficio. Otro estudio de ACTG se pregunta si incrementar los niveles del inhibidor de la proteasa tiene un impacto sobre la supresión viral. Es necesario observar el balance de la potencia del régimen en relación con cualquier aumento en la toxicidad: Se verá comprometida la adherencia de los pacientes? Un pequeño estudio piloto comparó la utilización de cuatro tabletas de *Kaletra* (un total de 533 mg de lopinavir y 133 mg de ritonavir) con tres tabletas de *Kaletra*, dos veces al día, pero con el agregado de 200 mg adicionales de ritonavir (un total de 400 mg de lopinavir y 300 mg de ritonavir). Como era de esperarse, los resultados del estudio mostraron un incremento en la incidencia de efectos adversos, tanto eventos gastrointestinales como incremento en los lípidos—entre aquellos en el grupo que recibieron la dosis más baja de lopinavir, pero la más alta de ritonavir (una dosis de más del doble)

En otro estudio similar del que participaron individuos con múltiples mutaciones resistentes PI, también se elevó el régimen de proteasa a cuatro píldoras de *Kaletra*, en lugar de tres (533 mg de lopinavir y 133 mg de ritonavir) dos veces al día. Al menos con relación a los niveles de

droga esperados, la dosis más alta fue mejor: la posibilidad de alcanzar el objetivo de concentraciones de 5,500 ng/mL (que permite predecir una respuesta antiviral a largo plazo) fue más alta en el grupo al que se suministró la dosis de cuatro tabletas.

Lexiva y Kaletra un No-No?

Hasta ahora, ha habido escasos estudios definitivos que documenten la interacción antagonista entre lopinavir/r y amprenavir. Cuando estas drogas se usan en combinación, los niveles en sangre de las dos principales drogas que las componen (lopinavir y amprenavir) bajan a niveles peligrosamente ineficaces. Aunque evadir este combo es la manera más acertada de seguir, el monitoreo terapéutico de droga podría ser útil para indicar la dosificación en casos donde las opciones terapéuticas son escasas.

Los datos acerca de la interacción de lopinavir/r para la nueva versión de amprenavir (fosamprenavir o Lexiva en los EE.UU.—y por algún motivo, Telzir en Europa) son aún difíciles de obtener. Aunque amprenavir y fosamprenavir no son exactamente bio equivalentes, son los suficientemente parecidos en su aspecto químico como para constituir ambos una señal de alarma. En lo que se refiere a las interacciones, se han observado escasas diferencias entre los dos. Dadas sus complejas interacciones, si

fuera necesario utilizar esta combinación, probablemente sea una buena idea realizar monitoreos terapéuticos de droga para corregir cualquier desequilibrio en las dosis ya ajustadas. †

Por favor, dirigirse a nuestra web-site: www.aidsinfonyc.org/tag para obtener la versión completa de la información de Rob, con tablas y cuadros (tanto para las cifras de statins como para las de media-vida de tenofovir), †

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