TAG line
From the Treatment Action Group (TAG):
A monthly paper of research and policy
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Dismal Science

Squandering Public Goodwill and Scarce Research Funds To Boot; But To What End?

Altruism betrayed

On September 23, 2004, the US Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee held a hearing to discuss the ongoing "prime-boost" Phase III HIV vaccine trial in Thailand. Documents from the meeting-including a full transcript, background information about the trial and the FDA's current position on it-are available online on the CBER website www.fda.gov/cber/ TAG submitted the following testimony to the hearing, prepared by Richard Jefferys.

The phase III trial currently before the committee has been a subject of controversy, as outlined in the background document prepared for this meeting by FDA. The Treatment Action Group (TAG) has serious reservations about RV144 and the decision by FDA to allow the trial to proceed as currently designed.

Can you prove the concept of the trial without an ALVAC-only arm?

Perhaps the most significant concern regarding RV144 is the single arm design that will not allow the relative contributions of the two

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Panel Embraces Rx Interruption

"[Single episode treatment interruption] may be offered to patients with immune reconstitution, although participation in a controlled trial would be preferred... The long-term safety and efficacy of this approach are not known."

Source: "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, US DHHS. Updated 10/29/04. (see table, page 7)

Caveat Lector, The Sequel

Tangle of Interests and Disclosure Omissions Cracks Authors' Case For Early, Aggressive Treatment

* * *

'Treatment perfected'

* *

Parallel realities, of sorts, presented themselves last month to medical literature news junkies—which include a goodly share of the TAG team. Consider this December entry into the public conversation vis-à-vis the recently resurrected 'When to start?' debate:

The journal: U. Chicago's highly esteemed Clinical Infectious Diseases (sister journal to the more well known, Journal of Infectious Diseases or "JID")

The paper: "The Case for Earlier Treatment of HIV Infection," a review article which appeared in the December 1, 2004 issue.

The authors: Diane Havlir (formerly of UCSD and now at UCSF), Frank

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Taylored Treatment

Brown University Clinician Leads the Way In Providing Competent Care To Coinfected Injectors

Directly observed peg-INF?

A majority of the estimated 4 million hepatitis C virus (HCV) infections in the United States result from injection drug use with shared, unsterilized equipment. Coinfection with hepatitis C is prevalent among people who acquired HIV from injection drug use; up to 90% are coinfected with hepatitis C. Among HIV-infected persons in the United States overall, 25% are believed to be co-infected with HCV. (The rate of HIV/HBV coinfection in the U.S., by contrast, runs at around 10%.) In other countries, HIV/HCV and HIV/HBV coinfection are even more prevalent. Tracy Swan reports.

Before 1996, most coinfected people died from complications of AIDS before end-stage liver disease developed. Since highly active antiretroviral therapy (HAART) has greatly increased survival, hepatitis C coinfection has emerged as a significant contributor to morbidity and mortality as HIV accelerates hepatitis C disease progression and increases the risk for antiretroviral-induced hepatotoxicity. End-stage liver disease has become a leading cause of death among people with HIV and hepatitis C.

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vaccine components (ALVAC vCP1521 and AIDSVAX B/E) to be evaluated. A previously planned trial, HVTN 501, would have compared the effects of a similar ALVAC vector alone to ALVAC+AIDSVAX. This trial was cancelled due to the poor immunogenicity of the ALVAC vector which would have prevented the study from achieving its main goal, which was to assess CTL responses (as measured by interferon-gamma *ELISpot*) as a correlate of protection.

In the absence of HVTN 501, a successful outcome to RV144 would require additional phase III studies to tease apart the roles of the two vaccines in the observed protection. In other words, the concept that the trial is attempting to "prove" is that ALVAC-induced cellular immunity plus AIDSVAX-*induced* humoral immunity will be more protective against HIV infection than either approach alone, yet we have no idea whether ALVAC can offer any degree of protection against HIV infection (we do know that AIDSVAX alone—whether B/B or B/E—does *not*).

Lest it be assumed that the effect of adding AIDSVAX to ALVAC could only be additive, at least one study in macaques found that adding a gp120 protein boost to a vaccine designed to elicit cellular immunity resulted in a *poorer* outcome compared to the same regimen without the protein boost *(see SL Buge et al., AIDS Res. Hum. Retrovir. 10:891, 2003).*

To commit significant human and financial resources to a vaccine trial that cannot provide a definite answer to the question it purports to ask seems deeply foolish, particularly when there is widespread agreement that current funding for HIV vaccine research is inadequate. Based on this concern, TAG initially argued that the AIDSVAX boost should simply be dropped from RV144, allowing the study to definitively evaluate the protective efficacy of ALVAC vCP1521 *(see Science 305;5681:180, 2004).* Once volunteers began to receive AIDSVAX immunizations, however, this argument essentially became moot.

To commit significant human and financial resources to a vaccine trial that cannot provide a definite answer to the question it purports to ask seems deeply foolish.

Ethical Considerations

The Helsinki Declaration states: "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research."

TAG would argue that the benefits of participating in a phase III trial that can, at best, only lead to additional trials and cannot provide definitive answers as to the protective efficacy of the two vaccines involved are rather unclear. At the recent Bangkok meeting, it was stated that >70% of participants so far enrolled in RV144 cited "altruism" as their primary motivation, which leads to the question of whether the participants are aware that—even if successful—the trial will not be able to lead directly to the approval of an HIV vaccine for their population, or any other.

Politics & Science

TAG does not question the sincere and good-faith effort that many people (both in the U.S. and Thailand) have put into RV144 since the idea was first proposed towards the end of the nineties. However, the failure of the leadership behind the trial to adapt to the changing circumstances surrounding it reflects poorly on the trial's sponsors.

The cancellation of HVTN 501 and the failure of the two AIDSVAX efficacy trials should have prompted a more thorough review of RV144 than seems to have occurred, and this review should have included input from NIAID's advisory body, the AIDS Vaccine Research Working Group (AVRWG) and the FDA. Instead, input from the AVRWG was not solicited until after the study quietly began enrolling in October 2003. It is possible that this process was negatively affected by the politicking that surrounded the merging of the Military HIV Research Program back into the Division of AIDS at the National Institute for Allergy and Infectious Diseases (NIAID). TAG's understanding is that NIAID had to commit to supporting RV144 to completion as part of this merger, which presumably limits the ability of NIAID and its expert advisors to mandate substantive changes to the protocol.

AVRWG Recommendations

After a discussion at the January 2004 AVRWG meeting, a subcommittee chaired by Scott Hammer and comprising Larry Corey, Jerry Sadoff and ad hoc advisor Steve Self did review the RV144 protocol and made a series of recommendations aimed at improving the study, which were endorsed by the AVRWG as a whole. At the September AVRWG meeting in Lausanne, Jorge Flores presented the response of the RV144 investigators to each of the recommendations. Below is TAG's summary of the recommendations and

Letters to the Editor

Mike Barr and Rob Camp-

The article on the HIV websites and how their sponsors might influence their reporting is groundbreaking. TAG could do a great *Sunday New York Times* magazine piece using these tables as the essential structure -- with just a few interspersed comments and a little background.

The tipranavir article was good, but my frustration as a clinician is that I can't get what I regard as the most important information available on the tipranavir studies – information that would help me to optimize my use of the drug – anywhere. I can't get it from studies presented at the conferences. I can't get it from the news stories about the studies online. I can't get it in pharma sponsored throw away journals, or at pharma sponsored dinners -- where attendees are essentially paid to provide focus group type feedback but discouraged to raise any serious questions. And I can't get any of my colleagues to even recognize the question—which is not asked, much less answered even, in your otherwise good report.

Here it is again:

> Dear Sirs and Mesdames-
>
> Given that there is such a small percentage of patients who actually achieve undetectability with tipranavir -- even when used in combination with T-20; and given the wide range of T-cell and viral load entry criteria; and given that the patients who clinically really urgently need new drugs are not only least likely to benefit from these drugs but also most likely to blow these last remaining treatment options if ineffective; I would like more specific information, on a case by case basis, of the clinical histories of TPV/T-20 failures vs. responders.
>
> I would also like the patients stratified according to T-cell counts, HIV RNA, and number of active agents -- in terms of achieving or falling short of these endpoints. To not ask these questions before recommending tipranavir to an ill patient would be highly irresponsible of me. For you not to provide it is itself troubling.

Is there a place for a phone zap-like action pushing these issues to all the relevant parties -- certainly Boehringer and Roche/Trimeris, but also key people at FDA?

Roche finally has provided some of these data, but they seem to indicate that the patients who really need salvage therapy are not likely to benefit from it. After obscuring this information completely, they now have a new tactic: just take T-20 earlier! Real case histories as well as actual, specific, stratified data remain unavailable.

Paul C. Bellman, MD
New York

Dear TAGline,

Thank you for sending the latest issue. TAG's e-mail .pdf distribution system is a terrific innovation. The table examining the various sources of web-based treatment information was very useful. It's always interesting to see what consumers are reading, and I would like to see the results of your survey once it is complete.

I'm a little disappointed, however, that you picked up on Steve Miles' recent diatribe. I think Steve is very smart and hilariously funny, but this piece is too cynical (even for this former New Yorker). Other folks who you know well share this view. Instead of ranting and raving at Gilead, Steve should be going off on the FDA -- who are really the folks that insist on the TLOVR analysis and other stuff he talks about.

An ACTG researcher
(name withheld)

From: "Robyn Meyer" <Robyn.Meyer@mslpr.com>
Date: December 2, 2004 11:15:24 AM EST
To: <tagnyc@msn.com>
Subject: News Story: Roche and Trimeris Launch ASAP

Dear Mr. Barr,

I want to make sure you saw the press release from Roche and Trimeris announcing the launch of a new program called Fuzeon ASAP (Accelerated Simultaneous Access Program).

This program provides immediate access to Fuzeon for patients who are starting treatment with Fuzeon in combination with an investigational antiretrovial therapy obtained through an expanded access program. For patients enrolled in Fuzeon ASAP, Roche and Trimeris will provide up to a 60-day supply of Fuzeon at no cost to the patient.

For your reference, please find the attached press release. Please feel free to contact me with any questions.

Regards,
Robyn Meyer
212-468-3376

We welcome your thoughts and comments. E-mail us at tagnyc@msn.com, transmit a FAX at (212) 253-7923, or send us a letter at *TAGline* Editor, Treatment Action Group, 611 Broadway Suite. #608, New York, NY 10012.

responses (any errors are ours and further information should be sought from the AVRWG):

* **Recommendation**: Making protection against HIV infection and reduction in post-infection viral load co-primary endpoints of the trial, thereby potentially reducing the total sample size from 16,000 to 8,000 or less.

* **Response**:'Yes,' to co-primary endpoints. 'No,' to any reduction in sample size (in case there is a decline in incidence).

* **Recommendation**: Clearly defining the criteria used for post-infection viral load analyses.

* **Response**: 'Yes.'

* **Recommendation**: Providing immunogenicity data from a subgroup of vaccinees and controls to the Data Safety Monitoring Board (DSMB) in real time.

* **Response**: 'No,' but will consider enrolling an extra 200 people in order to conduct an immunogenicity study.

* **Recommendation**: Framing a futility analysis for use by the DSMB in order to ensure that the

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trial can be stopped if it is not going to meet the primary goals (e.g., due to insufficient endpoints or inadequate enrollment).

* **Response**: Criteria for stopping trial due to operational futility will be promulgated. Stopping rules based on scientific futility will *not* be developed.

In the apparent absence of any possibility of dropping the AIDSVAX component from RV144, TAG endorsed the original AVRWG recommendation as a reasonable attempt to address the shortcomings of a trial that was already underway. The fact that the RV144 investigators have chosen to only selectively adopt the recommendations is therefore profoundly disappointing. TAG encourages the committee to discuss these issues further with the AVRWG and the RV144 investigators.

Lessons for the Future

TAG strongly encourages the FDA to rigorously address the potential of any HIV vaccine efficacy trial to lead to licensure of a product (or products), regardless of the where the research is conducted. We also strongly believe that 'go'/'no go' decisions on moving vaccines into efficacy trials need to be based on the best available scientific evidence; it is notable that the International AIDS Vaccine Initiative recently announced that they will likely not move their DNA/MVA HIV vaccine candidate into efficacy trials due to poor T cell immunogenicity, yet the levels of immunogenicity achieved with this approach are comparable to those seen with the ALVAC vector under discussion today. †

Well, How Did We Get Here? A Timeline for the Initiation of the RV144 Prime-Boost Trial

1995-2001: U.S. Military HIV Research Program/Thai Ministry of Public Health collaboration tests various combinations of ALVAC prime/Env protein boost vaccines, eventually choosing to move ahead with the ALVAC vCP1521 vector boosted with AIDSVAX B/E.

July 2001: *Science* magazine's Jon Cohen breaks the story of the planned shift of the U.S. Military HIV Research program from the Department of Defense to the National Institutes of Health.

October - November 2001: IAVI Report article by Patricia Kahn cites phase III prime-boost milestones: "The final decision on launching Phase III testing will be based on whether results from an ongoing Phase II study (RV135) in Bangkok meet immunogenicity milestones."

January 2002: HVTN 501, a primarily US-based trial that would have compared the protective efficacy of ALVAC to ALVAC+AIDSVAX B/B and evaluated CD8 T cell responses as a correlate of immunity, is cancelled due to the fact that ALVAC did not induce detectable CD8 T cell responses in a large enough percentage of participants in a preparatory phase II trial.

July 2002: National Institute of Allergy and Infectious Diseases (NIAID) issues a release stating in part that: "NIAID, part of the National Institutes of Health (NIH), and the U.S. Army Medical Research and Materiel Command (USAMRMC) of the Department of Defense (DoD) recently signed an Interagency Agreement to transfer oversight and management of the U.S. Military HIV Research Program (USMHRP) to NIAID.

August 2002: The majority of members of the World Health Organization (WHO) and Joint United Nations Programme on HIV/AIDS (UNAIDS) Vaccine Advisory Committee (VAC) endorsed the proposed R144 trial and protocol (but not unanimously).

November 2002: WHO-UNAIDS consultation (conducted together with the U.S. Centers for Disease Control [CDC]) to discuss "Implications of forthcoming results from the first Phase III trial of an HIV vaccine for ongoing and future trials." They decide that if efficacy is not demonstrated in the AIDSVAX trials, proceeding with RV144 is appropriate "because of the independent scientific rationale of the prime-boost strategy."

December 2002: The report from the WHO-UNAIDS consultation was "presented to and accepted by" the WHO-UNAIDS Vaccine Advisory Committee. Minutes from this meeting are also not publicly available.

February 2003: Failure of AIDSVAX B/B to protect against sexual transmission of HIV infection reported.

September 2003: Screening for RV144 begins, the only public announcement in the U.S. is a brief, little-noticed release on the U.S. Military HIV Research Program's website.

October 2003: First RV144 volunteers vaccinated.

Please refer to the online version of the January TAGline *for a continuation of this RV144 timeline, as well as additional details and hyperlinks.*

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Until just two years ago, the NIH Consensus Statement on Management of Hepatitis C recommended that hepatitis C treatment be withheld from drug users until they had been drug-free for at least six months. A new Consensus Statement was issued in 2002, recommending that hepatitis C treatment decisions be made on an individualized, case-by-case basis rather than unilaterally withholding treatment from active drug users. Despite this guidance, substantial barriers remain for drug users seeking treatment for hepatitis C. There is little information about safety, efficacy, adherence strategies and management of side effects in injection drug users, regardless of their HIV status. The lack of research on optimizing hepatitis C treatment in injection drug users is outrageous, given that they are the highest-prevalence population.

The dearth of research may continue to support the rationale to withhold hepatitis C treatment from drug users. In the absence of data or specific guidelines for care and treatment of hepatitis C in coinfected people, many clinicians look towards recommendations from a panel of experts on care and treatment, the HIV-HCV International Panel. In January of 2004, the Panel's updated recommendations, Care of Patients with Hepatitis C and HIV Co-infection, were published in AIDS. The panel's recommendation that hepatitis C treatment should be provided to persons with "...no active consumption of illegal drugs" will create additional barriers for coinfected injection drug users.

It is crucial that we develop more effective ways to deliver care to coinfected injection drug users while researching methods to optimize HCV treatment outcomes in this population. A recent study from Anderson and colleagues reported that coinfection with hepatitis C significantly increased the risk of death among a cohort of 907 veterans. Coinfected persons were significantly more likely to be African American, and to have acquired hepatitis C through injection drug use. They were significantly less likely to have been prescribed HAART than cohort members with HIV alone. However, the investigators did not find a significant difference in CD4 cell recovery after initiation of HAART by HCV status, nor was HCV status associated with progression from HIV to AIDS.

Substantial barriers remain for drug users seeking treatment for hepatitis C.

Fortunately, a handful of clinicians in the United States are developing specialized outreach, care and treatment programs for people with multiple diagnoses—HIV, hepatitis C coinfection, drug and alcohol dependency and psychiatric illnesses. Lynn Taylor and her colleagues work at Rhode Island's Brown Medical School Immunology Center, which is known for developing innovative ways to provide treatment to disenfranchised populations.

They are treating people for HIV and hepatitis C as they struggle with homelessness, mental illness and addiction. Taylor and her colleagues deliver care to HIV-positive people in shelters, on the streets—even at donut shops, and the Rhode Island prison system. Until recently, Rhode Island's penalty for syringe possession was a sentence of up to ten years, which Taylor says "forced people to become infected with HIV and hepatitis C." Rhode Island's history of harsh penalties for injection drug use has made it home to an HIV/HCV coinfection epidemic. It is one of only four states where more than 50% of AIDS cases are associated with injection drug use. "We need to focus on bringing HIV and hepatitis C care to people who are incarcerated," says Taylor, "since in this country, people who have drug problems often end up in the correctional setting."

Brown's Project Bridge Program, which links HIV-positive prisoners with intensive case management services, housing, and comprehensive medical care could become the standard of care for incarcerated persons with hepatitis C instead of the current standard of care for hepatitis C, "you have hepatitis C, here's a referral to a physician who may or may not treat you or here's a prescription."

The resistance to treating coinfected injection drug users mirrors the attitude towards treating HIV in rural settings in the developing world. Many doctors have expressed doubts about treating injection drug users. Procedure-driven health care is more lucrative, and simpler, than caring for people who may not have stable housing, may be struggling with mental illness, the constant stress of illegal drug use, and HIV disease. Taylor recently addressed a group of gastroenterologists on hepatitis C treatment for injection drug users. Half of them walked out minutes after she began her talk; she overheard one saying "I don't want to hear about this" as he left the room.

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According to Dr. Taylor, there is "no justification" for withholding hepatitis C treatment from coinfected drug users, "until evidence says that it is harmful, it is not responsible to withhold treatment without data to support the rationale." Her program does not use abstinence from drugs or alcohol as criteria for hepatitis C treatment, nor is she currently using a threshold for CD4 cell count, although the International Panel recommends treating HCV only in persons with CD4 cell counts of >350/mL.

Taylor questions the Panel's CD4 cell threshold of >350/mL. Although early studies of standard interferon therapy found that HCV treatment was largely unsuccessful for a few coinfected people with CD4 cell counts of <200, recent trials of pegylated interferon-based therapy did not report an association between CD4 cell count and response to HCV treatment. This may be due in part to small sample size in each of the trials. Clearly, more research on hepatitis C treatment in people who have low CD4 cell counts is necessary.

At Brown's immunology clinic, 60% of 1,000 patients are receiving HAART. Half have CD4 cell counts of <350, and half of these have <200 CD4 cells. "We can wait and wait, but their CD4 cell counts may not rise quickly enough despite optimal HIV treatment," says Taylor. "What decision should be made about HCV treatment for a coinfected patient who has cirrhosis, a CD4 cell count of <150 and undetectable HIV RNA? Do we wait [to treat] until s/he has died of liver disease?"

Clearly, hepatitis C treatment in coinfected people with low CD4 cell counts merits more research, since finding patients in the recommended CD4 cell strata may be challenging. Since antiretroviral therapy is often prescribed to injection drug users later than to non-users, many start HAART at low CD4 cell counts. Initiating antiretroviral therapy at a low CD4 cell count is effective virologically—HAART can suppress HIV replication—but the CD4 cell count may not increase to the Panel's recommended threshold for HCV treatment. Taylor worries that a low CD4 cell count may be used as criteria for withholding reimbursement. "Is there clinical benefit or does CD4 cell count have an effect on histological response to hepatitis C treatment? I want justification for withholding treatment. Can you give us this?"

Hepatitis C treatment in coinfected people with low CD4 cell counts merits more research.

Taylor has a slew of ideas for research. She has used interferon therapy as a way to work with people about their drinking. "Several [people] have stopped using alcohol, but we have a small number of patients. A study would be great." She wonders about reproducing programs like hers, where weekly injections of pegylated interferon are directly observed, since "supervised HCV therapy allows us to address safety, adherence, access and efficacy when we see people, and unlike treatment for HIV, hepatitis C treatment is finite.

Directly observed therapy has been extensively studied for TB; it can be modified for hepatitis C treatment in multiple settings-medical offices, correctional facilities and methadone clinics. Ribavirin can be administered with the morning dose of methadone, and a nurse could come in once a week to give injections. Will optimizing adherence, tolerability, and safety for coinfected active drug users with supervised pegylated interferon translate into improved efficacy? What is impact of these interventions over time?"

Peer education has been an effective method for reducing risk behaviors of injection drug users, many of whom are reluctant to discuss illegal drug use with non-users. Taylor wonders what data are needed to create reproducible, peer-guided HCV treatment models for HIV+ patients. Does an HCV education program and peer support group help coinfected people make hepatitis C treatment decisions and increase treatment readiness? What impact does hepatitis C education and peer support programming have on adherence to hepatitis C treatment and completion of treatment? Could a peer-driven program be effective for alcohol cessation?

Drug users, activists and like-minded researchers must come together to craft a research agenda. Manufacturers of hepatitis C therapy need to support this research. The failure to support research to optimize treatment of hepatitis C among the highest-prevalence population is unacceptable, and would not be tolerated in another condition. In Taylor's words, "Do cancer doctors give chemotherapy and say come back in three months? We need to be just as present and compassionate with HCV treatment as we are with cancer." †

Late 2004 Changes to Federal (DHHS) Treatment Guidelines

Viral load threshold for initiating antiretroviral therapy in asymptomatic individuals with CD4 count >350

Old threshold: 55,000 copies/mL
New threshold: 100,000 copies/mL

Recommendations for interrupting treatment in individuals with relatively successful viral control

Old advice: There was none--except to warn against it.
New advice: A full page and a half of considerations, evidence (and warnings against the lack thereof). "This option (treatment interruption and reinstitution based on CD4 cell count) may be offered to patients with immune reconstitution, although participation in a controlled trial would be preferred. The long-term safety and efficacy of this approach, however, are not known."

Coming to terms with stavudine (d4T/*Zerit*)'s association with lipoatrophy (especially facial) and other side effects

Old advice: Stavudine (d4T/*Zerit*) was listed among "preferred" components of first-line therapy.
New advice: Stavudine (d4T/*Zerit*) has been sidelined from "preferred" to "alternative" nuke option.
(Comment: Now in line with British HIV Association (BHIVA) guidelines, albeit 2 years later.)

Coming to terms with Trizavir (AZT/3TC/ABC)'s lack of efficacy

Old advice: Should only be used where other options may be less desirable due to concerns over toxicities, drug interactions, or regimen complexity.
New advice: Not to use except when no other acceptable regimens for patient

Recommendations for adjunctive use of hydroxyurea

Old advice: "Should not be offered at any time"
New advice: Something along the lines of, 'Not within our purview' *(aka 'too hot a potato for our hands')*
Okay, in the august panel's trenchant prose: "It is the opinion of the Panel that discussions in the guidelines should limit themselves to commentary on FDA-approved agents that are indicated for the treatment of HIV infection... and thus [hydroxyurea] will not be discussed in this guidelines document."
(Comment: Guidelines writing as an Olympic sport! Some sort of acrobatics award is clearly in order here.)

Resistance testing in individuals on treatment

Old advice: Only results from testing done while patient still actively taking the drugs in question are meaningful.
New advice: Resistance testing can be successfully performed on blood samples drawn within 4 weeks of drug discontinuation (of drugs in question).

Baseline resistance testing for drug naïve chronically infected individuals considering starting antiretroviral therapy

Old advice: "It may be reasonable to consider such testing, however..."
New advice: Baseline resistance testing recommended

Source: *"Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents," US Department of Health and Human Services (DHHS). Updated October 29, 2004 and available online at www.aidsinfo.nih.gov.*

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Palella (Northwestern U.), Scott Holmberg (CDC), Ken Lichtenstein (Rose Medical Center, Denver, CO)

The conclusion: With the advent of easier to take, less toxic antiretrovirals, physicians may want to start treating asymptomatic individuals at CD4 cell counts above the currently recommended 350 threshold.

Quotable quotes: "We note a growing body of evidence suggesting that earlier treatment with newer, better, and safer drugs is associated with improved survival, more effective immune-system improvement, less toxicity and drug intolerance, and other clinical and public health benefits."

"We think that the issue of toxicity, a frequent reason that clinicians delay therapy, needs reconsideration."

"The list of novel drugs available for inclusion in 'salvage' antiretroviral therapy regimens continues to grow."

Presented as it was in CID, the weight of the authors' collective prestige lends an element of credibility to an argument that might otherwise be greeted with a deservedly familiar skepticism. "Have *Viread* and *Reyataz* really altered the therapeutic landscape so much that we must now revisit the age old question of when best to start treating asymptomatic individuals? According to these Key Opinion Leaders, it has. But wait, the plot thickens.

The journal's conflict of interest disclo-

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sure policy requires authors to list any financial relationships with drug and diagnostics companies that could be perceived as prejudicial to their judgment. The authors thus complied by submitting the following:

Potential conflict of interests: "FJP has served on speakers' bureaus for Bristol-Myers Squibb, Gilead Sciences, and Roche Pharmaceuticals. All other authors: no conflicts."

As a reader, it's one thing to come across this provocative pitch (access to which was made free to the public and then basically parroted on all but one or two of the HIV websites) accompanied by the requisite footnotes indicating if and where the authors might have something to gain from their interpretation of the literature. Dr. Frank Palella (and in a companion editorial commentary, Drs. Brian Boyle and Calvin Cohen, where they "yearn" for the day when all HIV+ people are on 100% suppressive therapy) is to be recognized for his candor. The larger question is whether it is appropriate for physicians who have been supplementing their income (sums conceivably rising to the low six figures annually) by doing traveling shows on behalf of the makers of *Reyataz*, *Truvada* and *Fuzeon* to be authoring papers where no new data are presented and where no peer-review occurs.

That same candor was missing for two of the paper's other co-authors. Hadn't Dr. Diane Havlir, Doug Richman's UCSD protegée, reported a string of consulting gigs for Tibotec and ViroLogic in Richman's throw-away journal *Topics in HIV Medicine* a short while back? No mention of them here. BMS, Gilead, and Glaxo have also been generous to Havlir's program—a disclosure she was required to make earlier in 2004, but not in CID.

Researchers, understandably, only grudgingly make these details public, regarding quarter-column length financial disclosures as a tad embarrassing. (At the ACTG, FDA AVAC and the PHS guidelines panel, for example, this information, although requested, is treated top secret and carefully guarded in-house.)

Not to be outdone, Dr. Ken Lichtenstein turns out to sit on the advisory boards (a prized post in the pharma consulting world), of BMS, Glaxo and Gilead—as well as a spot on the traveling lecture circuit for Abbott and Merck. None of these was mentioned in the CID article.

One might ask what purpose these essentially voluntary (and easily finessed) disclosure requirements serve if (A) the journals don't bother to vet them and (B) those potentially in hock up to their stethoscopes (should they ever find time to don one) are allowed to live these double lives and then carry on with business as usual. Mightn't it be time to give them some teeth? In this particular case, what will it take for reputable journals such as CID to reconsider its position on allowing physicians with these sorts of conflicts of interest to author editorial and review articles—where no new data are presented? The *New England Journal* and *JAMA* have had clearly defined restrictions in place for years.

Transparency in these matters is vital, as the guidance and sway of these pharma funded talking heads exert a powerful and under-appreciated influence on not only the course of AIDS research and drug development efforts but, perhaps more importantly, also on the evolution of clinical care and the long-term well-being of all HIV-positive people struggling to stay alive and well. †

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