**XI IRTT**

**Why the Tap ‘n’ Drainers Have Always Been Wrong; Plus, A New Theory About MDR HIV**

Primacy of immune activation

Project Inform, the country’s longest serving community-based AIDS treatment information organization, has been sponsoring scientific think tanks on immune restoration since 1992. Their Immune Restoration Think Tank (IRTT) is also known as the ‘Dobson Project’ in honor of the prime mover behind the early meetings, the widely respected and much-loved San Francisco AIDS activist Jesse Dobson, who died on September 23, 1993. After a hiatus since the last meeting in Chicago in 1999, Project Inform recently held the ninth IRTT at the Nikko Hotel in San Francisco. A full official report of the meeting, including recommendations regarding future research priorities, will be produced by Project Inform and made available on the IRTT section of their website. This article, by Richard Jefferys, will just touch on some of the interesting talks given particularly by immunology researchers attending the meeting.

Zvi Grossman from the National Institutes of Health shared some thoughts regarding pathogenesis, focusing on the conundrum that has faced the field since the very...— continued on next page —

**Questioning the Firewall**

“If you have a genuine firewall between the editorial and sales sides of your treatment magazine or website, you would be extremely unusual. For most journals and magazines, the pharma marketing people call the shots.” (see page 3)

Marcia Angell, MD

“The Truth About the Drug Companies: How They Deceive Us And What To Do About It,” (Random House, 2004)

**Dogs and Ponies**

**Mixed Results (and Lots of Diarrhea) for the Tipranavir Studies; Plus Salvage Study Designs for JNJ/Tibotec’s PI and Non-nuke**

‘Boosting to break the bank’

Boehringer Ingelheim filed its new drug approval applications for tipranavir in the United States and the European Union last month. The plan is to receive U.S. FDA imprimatur by May 2005 and a green light by Europe’s EMEA by late summer. Meanwhile, JNJ/Tibotec’s protease inhibitor and non-nuke me-toos head into their final lap. (If only they had something innovative and truly useful. But then, the same could be said of BI. Remember when that crazy Kalamazoo outfit was trying to figure out what to do with tipranavir—way back in 1998?) Rob and Mike stitched together this short update.

**Update on Tipranavir (ok, TPV/r)**

BT’s two pivotal trials for tipranavir...— continued on page 6 —

**Truvánadu**

**Does Gilead’s Famed 903 Study Really Show You What They Tell You It Shows?**

“Tenofovir/FTC Is Superior to Combivir!!” Is this really believable? Or how about “AZT/3TC equals ABC/3TC”?? Of course not. But you are led to those conclusions by the way the clinical trials are designed. There is an old adage, “How do you survive a fall out of the Empire State Building? Jump out the first floor.” So too with clinical trials.

**Gussying Up the Bird for the Prom or How to Make Pigs Fly**

So if you’re a drug company, how do you make your drug look good? Simple, combine it with efavirenz or nevirapine and then compare it against another arm similarly configured. Then run the trial for an inadequate time interval, say 48 weeks, and under power the trial for any meaningful difference.

If you really want to stack the deck, allow subjects to enroll with all stages of HIV disease. This will ensure a low mean HIV copy number. Since the heavy lifting is done by efavirenz or nevirapine, your drug will nearly always be equivalent or at least “non-inferior.” Hell, my guess is that in this population Holy Water plus 3TC plus an NNRTI versus didanosine plus 3TC plus a non-nuke would show that...— continued on page 5 —
Homeostasis is a word used to encapsulate the ability of biological systems to generally maintain a balanced steady state; in the case of memory T cells the human body can accommodate (which is thought to be around 1-2 trillion).

Because the memory T cell pool fills up rapidly in infancy, the new cells that are subsequently generated by encounters with new pathogens have to displace existing cells in order to survive. Grossman hypothesized that if the generalized immune activation seen in HIV infection generates memory T cells at an accelerated rate, one consequence would be that existing memory T cells—such as those targeting common opportunistic pathogens like PCP, CMV, et cetera—are at risk of being displaced. Such a phenomenon could potentially explain the decline in immunity to opportunistic infections that eventually leads to AIDS. On other hand, Grossman suggested it could be beneficial to look for ways to displace HIV-infected memory CD4 T cells with uninfected, functional memory CD4 T cells.

Since David Ho first proposed his simplistic ‘tap and drain’ theory of CD4 T-cell depletion in 1994, numerous studies have shown it to be wrong.

Grossman pointed out that the question of whether HIV can directly destroy CD4 T cells is almost moot since the virus preferentially targets activated T cells, the vast majority of which are short-lived and die within a matter of days. To illustrate the point, Grossman suggested comparing the kinetics of HIV viral load declines in individuals starting HAART to the kinetics of activated T cell death at the end of a primary immune response.

In a typical immune response (to a virus such as influenza, for example), T cells that recognize the pathogen become activated and copy themselves (proliferate) in order to generate a swarm of short-lived “effector” T cells that all recognize the same pathogen. These activated effector T cells migrate out from the lymph nodes (where activation occurs) in order to hunt down and eliminate or control the pathogen. Within a few days, the vast majority of these cells (~95%) will automatically die in a process called apoptosis or activation-induced cell death. A minority of the effector T cells will survive and return to a resting (non-activated), long-lived “memory” state; these cells normally maintain the ability to proliferate and generate a new swarm of effector T cells if the same pathogen is subsequently reencountered. Grossman noted that when HIV replication is controlled by the initiation of HAART, the two-phase drop in viral load (a rapid decline in the first few days followed by a slower decline over several weeks to months) mirrors the initial rapid death of activated effector T cells followed by the return to rest of surviving memory T cells.

Grossman and immunologist William Paul have proposed that one effect of persistent HIV-induced immune activation is to slowly chip away the number of T cells that are able to deactivate and return to a resting state, thereby slowly depleting the T cell pool (see Nature Medicine, 8:4:319-323, 2002). Grossman also highlighted HIV’s ability to persist in a latent state in some resting memory CD4 T cells, producing a reservoir of virus capable of renewed rounds of replication if the infected resting CD4 T cell gets reactivated.

A particularly novel aspect of Grossman’s talk focused on memory T cell homeostasis.
4. Who provides you with up-to-date treatment information?

Popular treatment information resources for doctors and patients—and their reliance on pharmaceutical largesse

[Self-test: Inquire for yourself from those resources on which you most rely. Ask to see their business model. Looking for amusement on a cold, wet winter’s day? Match top billing conference summary headlines to the sites’ major sponsors. Answer key to come in 2005. TAGline will also try to get an interview or two with some of these sites’ overlords.]

Medscape.com
Bangkok (and ICAAC 44) conference coverage paid for by Bristol-Myers Squibb, GSK, Gilead and Pfizer. (Medscape’s recent scrolling banner had one multi-PI resistant activist type misty eyed with nostalgia: “A drug you’ve trusted for years... deserves a second look.” The lucky recipient of this extreme makeover was, alas, Invirase. And an 11th hour email ‘blast’ to Medscape subscribers (World AIDS Day eve) pitched an interview with DHHS guidelines panel chair John G. Bartlett on the October ‘04 updates. The breathless summary mentions tenofovir ELEVEN times within a single page of text, squeezes in an argument for earlier treatment initiation and somehow glosses over the panel’s lifting of the block against the use of hydroxyurea.)

Pharma (or pharma consultant) sign-off on CME content? __ Yes __ No __
Sign-off (or assignments) for conference summaries? __ Yes __ No __
Pharma (or pharma consultant) selection of authors/reporters? __ Yes __ No __

TheBody.com
Bangkok (and ICAAC 44) conference coverage paid for by Abbott, Boehringer Ingelheim, Gilead, GSK, and Roche/Trimeris.

Pharma (or pharma consultant) sign-off on CME content? __ Yes __ No __
Sign-off (or assignments) for conference summaries? __ Yes __ No __
Pharma (or pharma consultant) selection of authors/reporters? __ Yes __ No __

ClinicalOptions.com (and its imedoptions.com sister site)
Bangkok (and IDSA and ICAAC 44) reporting and CME sponsored by BMS, Pfizer, Roche/Trimeris, Boehringer Ingelheim.

Pharma (or pharma consultant) sign-off on CME content? __ Yes __ No __
Sign-off (or assignments) for conference summaries? __ Yes __ No __
Pharma (or pharma consultant) selection of authors/reporters? __ Yes __ No __

hivandhepatitis.com
Grants from Abbott, Gilead, Advanced Biological Labs, Ortho, Boehringer Ingelheim, Roche Diagnostics, BMS, Roche, GSK, Serono, Schering-Plough, Tibotec/Virco. Of interest, the top story on their site in November was the Havlir et al. review article from CID: “The Case for Earlier Treatment of HIV Infection.” Purely by coincidence.

Pharma (or pharma consultant) sign-off on content? __ Yes __ No __
Sign-off (or assignments) for conference summaries? __ Yes __ No __
Pharma (or pharma consultant) selection of authors/reporters? __ Yes __ No __

aidsmap.com
Link from home page directs users to complete list of funding sources: http://www.aidsmap.com/en/about/funders.asp. Conflict-of-interest concerns are acknowledged up front, and a brief paragraph explains that the service tries to diversify its funding as much as possible. Among its many underwriters, however, figure the usual pharma companies: Abbott, BMS, Boehringer, Gilead, GSK, Merck, Roche, Shire. Pharma currently makes up 22% of its funding—still a hefty chunk (smaller, I’m told, than that of TAG), but the aidsmap team is the most transparent of all the treatment information resources surveyed.

Pharma (or pharma consultant) sign-off on content? __ Yes __ No __
Sign-off (or assignments) for conference summaries? __ Yes __ No __
Pharma (or pharma consultant) selection of authors/reporters? __ Yes __ No __

HIVinsite.com
Grants from BMS, Boehringer Ingelheim, Gilead, GSK, Ortho, Pfizer/Agouron, Roche, Schering Plough—and Sun Microsystems and The Stempel Foundation.

Pharma (or pharma consultant) sign-off on content? __ Yes __ No __
Sign-off (or assignments) for conference summaries? __ Yes __ No __
Pharma (or pharma consultant) selection of authors/reporters? __ Yes __ No __

Poz magazine (Poz.com)
General magazine content, while bursting with HIV drug and nutriceutical ads (and more recently, those premium drug company wrap around outside covers—and a blazing BMS scrolling banner at its web site: “Ask your doctor about Reyataz.”) is said to be uninfluenced by its sole reliance on pharma (and nutritional company) funds for operating revenue. Content of Poz “special supplements,” however, is generally planned and written under close supervision of the pharma sponsor of that supplement’s topic. (The magazine was recently sold and the HIV+ activist publisher forced out.)
Deeks results strongly suggest that the maintenance of multi-drug resistant virus is beneficially altering the balance between the immune system and HIV.

Deeks compared the levels of T cell activation among 86 individuals with multi-drug resistant HIV compared to 13 untreated people with non-resistant or wild-type HIV; after controlling for viral load levels (and other factors known to impact activation such as hepatitis C co-infection), the degree of T cell activation was significantly lower for both CD4 and CD8 T cells in the individuals with multi-drug resistance. Taken together, Deeks results strongly suggest that—at least in this cohort—the maintenance of multi-drug resistant virus is beneficially altering the balance between the immune system and HIV. Deeks plans to conduct prospective studies to explore whether this apparent benefit can be further improved upon.

There were many other interesting presentations and discussions at the XI IRTT that will be included in Project Inform’s full report, including “surprising suggestions” that some familiar but non-HIV-specific drugs (imatinib mesylate aka Gleevec, and valproic acid, for starters) may deserve to be studied for their potential to target the reservoir of latently infected CD4 T cells. TAGline will alert readers when the report becomes available.

--- continued from page 2 ---
which the chromosomes of the cell (containing the genetic blueprint of the cell, DNA) grow and become prepared for the process of cell division (the splitting of the T cell in two to produce a new T cell)

• The subsequent S phase is when an extra copy of the T cell’s DNA is made in preparation for the generation of the new T cell.

• G2 is the final stage of preparation for the splitting of the T cell in two (the technical name for the split is mitosis).

• The final M phase stands for mitosis, when the new daughter T cell is produced.

Sieg used the radioactive label BrdU to identify S phase T cells in samples from HIV-infected individuals. He found that a greater proportion of CD4 T cells were in S phase than CD8 T cells, which may be an interesting finding given that when other markers of T cell activation are used more CD8 T cells appear to be activated than CD4 T cells. The frequency of S phase T cells correlated with viral load levels. Both the CD4 and CD8 T cells in S phase displayed similar external markers: the activation molecule CD38 (but not two other potential markers of activation, CD25 and CD69), CD62L and CCR7 (two molecules associated with trafficking to the lymph nodes and generally found on resting, not activated, T cells) and CD45RO (a marker commonly used to identify memory T cells).

The S phase T cells also expressed high levels of caspase 3 (an enzyme associated with apoptosis) and low levels of bcl2 (a molecule associated with T cell survival), suggesting that these cells are indeed short-lived. Preliminary efforts to evaluate the specificity of the S phase T cells (i.e., which antigens they respond to) are underway. According to Sieg, results so far indicate to be targeting antigens from HIV.

although these analyses may be complicated by the tendency of recently activated T cells to temporarily downregulate the receptor they use for recognizing antigens (the T cell receptor or TCR). Sieg stressed that this work is ongoing and more detailed results will eventually be presented and published.

San Francisco’s redoubtable Steve Deeks gave a rapid-fire update on his work with individuals who appear to experience treatment failure (as defined by increasing viral load and drug resistance) without showing signs of immunological or clinical disease progression. Deeks is investigating the possibility that HIV-specific T cell responses are contributing to the lack of progression seen in this cohort, and planning studies designed to evaluate whether immunological control of HIV replication can be enhanced in individuals with multi-drug resistance and limited antiretroviral options.

Deeks followed up on recent reports indicating that HIV-specific CD4 T cells capable of producing IL-2 or IL-2 and interferon-gamma may play a role in controlling viral replication (see TAG’s September 2003 Basic Science Review) by evaluating these responses in individuals with partial control of viral load and multi-drug resistant viruses who remain on HAART (which he calls “PCATs” for partial controllers on antiretroviral therapy). Compared to individuals with progressing disease, PCATs had significantly greater numbers of IL-2-producing HIV-specific CD4 T cells, as did untreated individuals with long-term non-progressing infection (LTNPs). PCATs also had significantly lower levels of T cell activation (as measured by CD38 expression).
and put it in both arms. That is step one. Then add comparator drug (or drugs) to each arm that differs little in potency. That is step two. Stir, never shake, and voilà! You have a trial that will go on forever, is guaranteed to show equivalence (or, if your drug is really terri-

This nonsense certainly did not start with Gilead—although they have surely perfected its use in recent years.

It's Big Business, This Delusion Game
So too with the design of these “clinical” trials. The only thing clinical about them is the surgical precision with which they render their lobotomy. How else can you explain our sheepish behavior? Drug companies, and in particular the marketing departments that run them, design these trials deliberately with these endpoints in mind. They know that efavirenz, nevirapine and other NNRTIs are well tolerated and potent drugs. They also know that, in order to observe a durable response, all one needs to do is to “surround” them with a drug (or drugs) that provides a modicum of protection in the form of antiviral resistance mutations. That is all that is necessary to be successful. So you take efavirenz or nevirapine or you were cheap/stupid, “non-inferior”), and the marketing department will be happy. Our drug is just as good as theirs! Then you can spend your millions spinning yarn about how your drug is better tolerated or less hated—or both, as the case may be.

You Fell for It Again—Oops!
This nonsense certainly did not start with Gilead, although they have surely perfected its use in recent years. The Gilead design of its 903 trial is a classic example: d4T/3TC versus tenofovir/3TC with EFV. Glaxo also chose it for the design of CNA30024: Combivir versus ABC/3TC with EFV. And now it seems, Gilead is back at it again with a comparison of “Truvana” vs. Combivir with EFV. When will all the nonsense stop? It makes me wish I could just listen to old MP3s of Bush 43 speeches. Then at least I’d have a reason for my insanity.

But seriously, Gilead must be at week 6 billion and counting still looking for a difference between its two arms; all the while merrily reporting how their drug has fewer problems. “See, what did I tell you?” At least with this Glaxo study, the GSK marketing geniuses gave up after a while since they only wanted to show that their drugs were equivalent (which this study did NOT do: it only proved that their drugs were not woefully inadequate in the presence of efavirenz.) Big deal, so is Holy Water!

TLOVR and Other Made Up Nonsense
And thanks to the rocket scientists at the FDA who made up a new term called TLOVR, Gilead can now go around trumpeting that Truvana is statistically better than Combivir at 24 weeks. It is NOT. Why? Because for those who really care, TLOVR is a made-up statistical censoring technique that punishes you when a subject drops for intolerance, among other reasons.

So the term “Time to loss of virologic response” is actually not loss of virologic response at all but really “time to first censoring of subjects for any reason after a virologic response.” But then you knew that, right? You are smart. You went to medical school. You buy generic brand toothpaste, and you won't be fooled. Right? Pigs don't actually fly, right? George Bush didn't win, did he?

Dr. Steven Miles is an old friend of TAG (old as in ‘longtime’) and a founding member of the ACTG (although the ACTG leadership may regret having invited him to the party.) He's also a great guy to take out to lunch. More of his writings can be found at his website, www.hivmedicine.md. (It didn't escape our attention that the site is underwritten by the likes of Ortho, Abbott, Boehringer Ingelheim, BMS, Chiron—and Glaxo. But he seems to have retained his delightful objectivity for now. The Gilead loan sharks don't appear to have gotten to him yet, and he probably shouldn't hold his breath for any near-term funding.) TAGline thanks him for permission to reprint.
TPV/r had a viral load reduction of >1.0 log vs. 22.3% on other PIs. At RESIST-1: 24-week results
90% male, 21% black. In both RESIST studies, 80% of people were on tenofovir, 60% on 3TC, 30% on ddI. The average viral load at baseline was over 5.0 log (that's 100,000 copies). All study participants were PI resistant, with an average of 15 protease mutations as well as having previously used an average of 12 antiretrovirals.

Baseline demographics
In RESIST-1, participants were 90% male, 21% black. In both RESIST studies, 80% of people were on tenofovir, 60% on 3TC, 30% on ddI. The average viral load at baseline was over 5.0 log (that’s 100,000 copies). All study participants were PI resistant, with an average of 15 protease mutations as well as having previously used an average of 12 antiretrovirals.

Both RESIST studies compare TPV+ritonavir (ritonavir at a total daily dose 400 mg) to what is called the “comparative PI+ritonavir” or CPI/r. Protease inhibitors used in the CPI/r group were: lopinavir 61%, saquinavir 20%, amprenavir 14%, indinavir 4%. RESIST-1 enrolled 311 people in the TPV/r group and a total of 309 on the various CPI/r regimens.

RESIST-1: 24-week results
41.5% of study participants on TPV/r had a viral load reduction of >1.0 log vs. 22.3% on other PIs. At week 8, 42% of tipranavir participants achieved log reductions of 1.4 log or greater, but at week 24 this reduction was only 0.88 log.

At week 24, 35% of TPV/r people had viral load <400 copies/ml (25% under 50 copies) compared to 17% of those taking CPI/r reaching <400 (vs. 10% under 50). Median viral load drop at week 24 was 0.88 log for TPV/r vs. 0.28 log for CPI/r. There was an increase of 36 CD4 cells at week 24 in the TPV/r group compared to an increase of 6 CD4 cells in the CPI/r group.

By week 24, 28 people (9%) had discontinued TPV/r due to side effects (n=15) or virological failure (n=13). 33 people (11%) in the CPI/r group discontinued.

T-20 effect in RESIST-1
36% of RESIST-1 participants were taking T-20, 19% adding it as they started this study. T-20 takers were generally more ill than the average study participant and yet, at least in RESIST-1, fared better than average (33% <400 with TPV/r vs. 45% <400 with TPV/r + T-20). This “T-20 effect” was not observed in the CPI/r group, where the percentages of people who achieved a viral load <400 were almost identical: 10% without T-20 vs. 14% with T-20.

Interaction data
Both clarithromycin and fluconazole raise tipranavir levels. Maalox lowers tipranavir levels by 23%.

Side effects
Rates of diarrhea and nausea (all grades) were high, as were elevations in ALTs, cholesterol and triglycerides. Boehringer would recommend pravastatin, or low-dose atorvastatin for those who need it. (TPV/r raises atorvastatin levels some 9-fold.) Discontinuations due to adverse events were higher with TPV/r (9.3% vs. 5.2%) than with CPI/r. Discontinuations due to high ALT were 6% for TPV/r vs. 1% for CPI/r.

RESIST-2: 24-weeks
The 24-week results of RESIST-2 were presented at the 7th Drug Therapy conference (Glasgow, Scotland) in early November. The RESIST-2 study was almost identical in design to RESIST-1, but recruited volunteers from Europe and Australia rather than the Americas.

863 people were enrolled into RESIST-2. As in RESIST-1, study participants were required to have a viral load >1,000 copies/ml, with at least one primary protease inhibitor mutation from the group 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, 90M and two or more mutations at codons 33, 82, 84 and 90. Again, they were randomized to receive an optimized background regimen plus either tipranavir/ritonavir (500/200 mg) or a ritonavir-boosted comparator protease inhibitor (CPI/r), consisting of lopinavir, indinavir, saquinavir or amprenavir.

After 24 weeks, an intent-to-treat (missing=failure) analysis showed that 41% of the TPV group had a drop in viral load of more than 1.0 log from a median baseline of 58,900 copies/ml. This compared to 15% in the comparator group (p <0.001). The median drop in viral load was also larger in the TPV group (0.72 vs. 0.22 log, p <0.001). More individuals in the TPV group had viral loads <400 copies/ml (34% vs. 13%, p <0.001) and 50 copies/ml (23% vs. 9%, p < 0.001).

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Cell Therapy aka Therapeutic ‘Vaccine’ Surprise Announcement for World AIDS Day

Even the researchers admit any definitive conclusions must await more rigorous investigation. But on the eve of World AIDS Day the news of a possible novel, less onerous, and much more affordable approach to the treatment of HIV infection splashed across news sites worldwide. (Well, more in Africa, Asia and Europe than in the U.S. Three days into the weekend announcement, in fact, there was nary a word from the Gray Lady, the Washington Post or even the Wall Street Journal.)

An exciting if simplistic version of the story would go something like this: researchers in France announced that immunization of a small group of HIV-infected individuals with a personally tailored cellular therapy (sometimes called a therapeutic or treatment ‘vaccine’) resulted in CD4 cell rises and drops of plasma virus on the order of 80% which persisted for more than 3 months after only one series of immunizations. In close to half the study volunteers, levels of plasma virus dropped by over 90%, and these viral load reductions persisted for one year or more. Not only did CD4 cell counts ‘increase significantly’ (although no numbers are apparent in published paper) and plasma HIV RNA levels fall, but so did cell-associated HIV DNA, the virus’ genetic code that hides inside infected cells and instructs them to pump out more virus.

The cell therapy preparation was tailor made for each of the 18 individual study participants—from his or her own immune system dendritic cells along with a chemically inactivated form of his or her host HIV.

A more sober take on the published results might point out the following: The number of people in the study was very small and, more importantly, there was no control (or comparator) group. To be eligible for the study, people had to be off all antiretroviral therapy—and virologically ‘stable’—for six months. So how exactly were these individuals identified and recruited? And how might they have fared even without the cell therapy?

Co-investigators Jean-Marie Andrieu and Louis Wei Lu note that while trial volunteers’ plasma viral loads had been stable prior to immunization, they lost an average of 100 CD4 cells over those six months. Once they got the vaccine treatment, CD4 cell counts ‘increased significantly’—at least until the totemic Day 112. Which begs an additional question: what happened at Day 112? According to the Nature Medicine paper, CD4 cell counts began to fall (and “returned progressively to baseline” values) and viral control flagged in several individuals. Was this simply an artifact of the study’s design? Or had it something to do with the actual response to the therapy?

The only reported side-effect of the treatment was an increase in the size of peripheral (groin and armpit) lymph nodes, of 3- to 5-fold (from 0.33 cm at study entry to 1.50-1.70 cm days 28 to day 224—and 1.0 cm at one year).

The so-called “Good Responders” in the study, presumably the 8 of 18 who appeared to control virus for an entire year after immunizations, had entry CD4 cell counts of 450 cells/ml or greater—and, as previously noted, were controlling virus off ARV therapy for a full six months prior to study entry. So just how representative of the average HIV+ person in need of treatment were they? Finally, since each person’s therapy was hand tailored to his or her own virus and cells, it is unclear how this type of treatment could be rolled out on a mass scale anytime soon—even if it were to prove effective in broader testing. (Although Andrieu writes that the treatment could be available for ‘routine use’ before 2008.) Stay tuned. --MB


CD4 cell counts rose more in the TPV/r group than the CPI/r group (31 vs. 1 cell/mm3, p= 0.022). Fewer people taking TPV/r discontinued treatment (17 vs. 29). (RESIST-1 saw opposite results.)

T-20 effect in RESIST-2

Twelve per cent of the study participants in RESIST-2 were taking T-20 as part of their optimized background regimen. In contrast to the results from RESIST-1, the inclusion of T-20 did not cause a significant increase in the effectiveness of TPV/r: 38% of these participants had viral loads below 400 copies/ml, compared to 13% in the CPI/r group, while 23% and 5%, TPV/r and CPI/r respectively, had viral loads below 50 copies/ml. Grade 3 or 4 adverse events were similar in the two groups (14% vs. 12%), with diarrhea, nausea and vomiting being most common. People in the TPV/r group, however, experienced a greater incidence of laboratory abnormalities—particularly rises in cholesterol, triglycerides and the liver enzymes (ALT; 5% vs. 2%, p < 0.05; (AST, 4% vs. 1%, p < 0.05). This observation was consistent across both RESIST-1 and RESIST-2.

Tipranavir: The near future

The BI people say they haven’t been told if they will have an actual AVAC hearing with the FDA. Meantime, they are conducting a study of the pediatrics liquid in 52 kids, by age, 2-5, 6-11, and 12-18.

Tipranavir price

If TPV is priced according to its usefulness, a policy which hasn’t appeared to quite yet catch on, it would be given away virtually free—as T-20 should be. Meanwhile, Abbott says that it will give out ritonavir for free to those using the high-dose booster, the dose (200 mg twice a day) used in both RESIST studies. (This unusually high dose of ritonavir as a PI boost may be responsible for many of the side effects reported in RESIST, along with perhaps the general advanced clinical status of the participating population.) TPV devotees boosting with a lower dose of ritonavir will apparently have to pony up the cash. Abbott refers these people — continued on back page —
to its Patient Assistance Program. (But, duh, why not simply have your clinician prescribe the high-dose boost and give the extra ritonavir to AIDS FOR AIDS or some similar ARV access group?) BI says its having “coformulation” talks with Abbott, which Rob suspects will go nowhere. Abbott has never co-formulated with any other PIs. Why would they start with Boehringer?

ATAC and The Fair Pricing Coalition have formally asked all pharma companies to institute an immediate price freeze on their HIV (and HCV) medicines, as well as to institute a ‘smart policy’ regarding the pricing of new drugs. BI says it has personally passed this letter on to the Chairman of the Board.

Update on the TMC sisters
Tibotec (a division of Johnson & Johnson) is developing an NNRTI and a PI almost in parallel: TMC125 is the NNRTI and TMC114 is the protease inhibitor. Because of this fact, and perhaps because Tibotec is claiming that the non-nuke and PI me-too’s will work in people already NNRTI and protease inhibitor resistant, ATAC as well as some European clinicians (in a Lancet letter recently) are asking that Tibotec/JNJ look at the two drugs together in the same study. This would allow a person in a salvage situation to know a lot of the information needed, such as drug-drug interaction experiences, with the other drug as well as with other anti-retrovirals and other frequently used medicines in salvage situations.

TMC114 is a sulfa-based drug, and rash has been reported in up to 17% of people taking TMC114 full strength.

The folks at Tibotec have suggested a trial that would compare the now pedestrian Optimized Background Therapy (“OBT”) in combination with its NNRTI vs. OBT in combination with its PI vs. OBT in combination with both its drugs:

- OBT + 125
- OBT + 114/r
- OBT + 125 + 114/r

(Tibotec’s protease inhibitor must be given with small doses of ritonavir, so it frequently appears in writing as 114/r.)

Or you could throw Pfizer’s edgy CCR5 (still without a proper name and know only as UK471) blocker into the mix:

- OBT + 125 + UK471
- OBT + 114/r + UK471
- OBT + 125 + 114/r

But a study such as this, which essentially pits drugs from two separate companies (in this case JNJ vs. Pfizer) head to head, is unlikely to ever get off the ground. Rob says that the potential benefits of being able to throw an entry inhibitor into two of the study’s three treatment groups could be enormous. One little wrinkle, though: the proper dose of Pfizer’s UK471 has not yet been decided on. But Rob says the FDA would tend to recommend the lowest dose tested, which apparently has shown decent antiviral efficacy.

Tibotec/JNJ is still working out the best doses of its drugs as well, and the formulations have not been 100% established. Treatment activists are to meet with them—perhaps along with FDA reps—in early 2005. †

—— continued from page 7 ——