GMHC treatment ISSUES

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HIV and Host Genetics

Complexity and Contradiction

By Bob Huff

I vividly remember the moment I understood how complex the life cycle of HIV must be and how difficult it could become to find a cure. During a press briefing at the 1989 International Conference on AIDS in Montreal, Professor Jay Levy, of the University of California, San Francisco, was asked about the prospects for halting the devastation of AIDS. He said the course of the disease in any one person was due to interactions between the virus, the host and the environment. Host genetics were stable, viral genetics evolved, but the environment within the body could be manipulated with medicine. Science needed only to find some process necessary to HIV's survival and block it—without upsetting anything the host requires to remain healthy.

Is a new generation of therapies that act on virus-host dependencies on the horizon?

The first generation of HIV drugs targeted the virus itself. If they also affected some of the body's systems, that was a side effect. Now, as we learn more about HIV's dependency on the body's own cellular functions, a new generation of therapies that act on host factors may be on the horizon. One potential advantage to using drugs directed to host proteins is that viral resistance might become less problematic. While HIV's genetics are wildly error-prone and produce an abundance of mutations every day (and it only takes one successful mutant to launch a resistant strain), the genetics of the human cell are stable. If you can block a host target once, you should be able to block it again and again. Of course HIV may still find a way to mutate around the impediment. A new class drugs called CCR5 blockers are designed to keep HIV from interacting with a protein on T-cells that the virus must bind to before it can infect a cell. The drugs stick to CCR5 and interfere with HIV binding thereby restricting infection. But laboratory studies have demonstrated that, as with every other treatment tried to date, HIV can eventually produce a mutation that evades the obstacle.

So far, all evidence suggests that CCR5 can be blocked without causing harm to the host, which is great news. But the big challenge to using drugs that disrupt natural mechanisms is to make sure they only inhibit HIV's interactions with the system and leave the normal activities alone.

Everyone into the Pool

To complicate matters, while any one person's genes are stable, there may be important genetic variations between individuals in a population that influence how well a medicine will work. One drug may not behave the same in every body. This is because human genes evolve in a population the way viral genes do in a body, albeit

over a much longer period of time. This means there is diversity in our gene pool. Furthermore, each set of genes has a twin; with one coming from each parent. (This, as Bill Clinton knew, is the real meaning of sex.) The gene pairs are called alleles, but not every pair is identical. For example, most people have two working copies of the gene that makes the CCR5 protein that HIV uses to infect new cells. But some people have only one working copy, and a few have none. Because people without a working copy of the CCR5 gene can't make the protein, very few of them become infected. And those who have contracted HIV typically experience minimal disease progression; a CCR5 blocker would be wasted on them.

The virus hijacks natural mechanisms to do the work of transporting, reproducing and distributing itself.

Host genetics are increasingly recognized to play a role in everything from one's initial susceptibility to HIV infection, to the strength and durability of the immune defense the body can mount, the pace of viral replication and the seriousness of damage done over time, to the likelihood that drug therapy will be successful. A picture is emerging that shows the virus hijacking natural mechanisms at nearly every stage of its life cycle to do the work of transporting, reproducing and distributing itself. Yet we are only at the threshold of grasping the design and shadings of the system's complexity.

At the 11th Annual Retrovirus Conference, HIV's dependence on its host was the subject of a number of important presentations. Speaking at one of the final sessions of the conference, Amalio Telenti, an HIV researcher from the Institute of Microbiology at the University of Lausanne, Switzerland, offered a qualified vision of how knowledge about host genetics might increasingly affect care and treatment for people with HIV.

Biology used to be simple, said Telenti, describing a time when genetic researchers were content to look for the role of single genes that produced phenotypic traits such as blue eyes or fluffy coats. But the field has rapidly evolved as we increasingly understand that phenotype is the net result of many small contributions from multiple genes that shape the complex traits we see in life.

Many host determinants and environmental factors at many points of interaction cumulatively help determine the clinical course of HIV disease. Although many of these factors are still unnamed, acting in concert they are responsible for the wide variability in disease progression rates seen in populations. The time from infection to a serious state of AIDS can average ten years in an untreated individual, but can range from one year to possibly never for a few people. Telenti has modeled the contribution of alleles of various markers of disease progression on the rate of CD4 decline from 500 to 200 in members of the Swiss HIV Cohort. People with the common alleles progressed on average in 5.1 years; those with bad alleles progressed in 3.1 years and those with protective alleles in 7.7 years.

Since a newly diagnosed person may not need or want to begin antiretroviral therapy right away, Telenti proposes that it would be useful to be able to predict when treatment should be started. By analyzing certain host genetic determinants associated with the course of HIV disease, it may one day be possible to predict the slope of T-cell decline and estimate a date when treatment will become advisable. Some of these determinants of faster or slower progression include genes that affect co-receptor availability, such as CCR5, but there are many others with less dramatic impact, such as various HLA types and genes for immune system messengers such as IL10.

A whole host of other host factors come into play when antiretroviral therapy is thrown into the mix. With multiple, variant transport molecules at the gut, the liver and cell, each person will process and eliminate different drugs at slightly different rates and may have different susceptibilities to toxicity. Genetics can help explain the wide variability in drug concentrations that are observed in population studies, and may explain why, for some people, drugs can never quite control their virus.

Telenti says that at least 40 percent of the variance in infectivity and diversity between individuals with HIV may be due to host factors. But, he cautions, the data on most genetic associations represent modest effects with wide confidence intervals. No single polymorphism likely controls the master switch for progression. Yet some human proteins have the potential to grant virtual immunity to HIV.

So Close...Yet So Far Away

APOBEC3G is a recently identified host protein with the potential to offer innate protection from HIV by scrambling its genetic code. Unfortunately, a viral protein called Vif readily binds to APOBEC3G and defeats its anti-HIV properties. Immediately upon its discovery scientists began asking, could a drug be designed that blocks Vif or binds to APOBEC3G and stops Vif from shutting it down? Amazingly, there is only one amino acid standing between runaway HIV infection and nearly complete immunity to the

virus. Nathaniel Landau, of the Salk Institute for Biological Studies in La Jolla, discovered that if the negatively charged amino acid at position 128 of APOBEC3G changes to a positively charged amino acid, then Vif no longer binds and HIV is rendered harmless. Landau's team now plans to look for that mutation in long-term non-progressors to see if perhaps their natural defenses are impervious to Vif. Others will be looking for variant APOBEC3G in different racial and ethnic groups.

APOBEC3G would normally have a tremendous impact on viral replication rates but it is silent in the presence of HIV. Telenti says there are likely dozens of genes that influence the pace of progression, with the net outcome due to a balance between the influence of rapid and slow factors. Landau agrees. He suspects there may be many factors present in cells in low quantities that, if they were strongly expressed, could protect against the virus. One of these may be a host protein called TRIM5; a potential contributor to innate immunity that may explain why monkeys don't get AIDS. Matthew Stremlau, from the Dana-Farber Cancer Institute in Boston, has discovered a protective factor that prevents human HIV from establishing an infection in the simian host. HIV can attach to and enter a monkey's cells, but gets stuck before it has a chance to replicate its RNA. TRIM5 apparently stops the viral capsid from uncoating and exposing its genetic payload. Humans have a variant of

Higher Sustiva Levels Seen in Some African-Americans

Drug metabolism is highly complex and may be modulated by interactions between multiple enzymes and environmental factors. Although the CYP3A4 enzyme responsible for clearing many protease inhibitors from the system is best known, new enzymes and new interactions continue to come to light. And for every new metabolic player discovered there is the potential for genetic variability between individuals and populations to complicate treatment decisions.

In a slide session at the 11th Annual Retrovirus Conference, Heather Ribaudo, of the Harvard School of Public Health, reported on a study of the pharmacokinetics of efavirenz conducted by the AIDS Clinical Trials Group (ACTG). The study, ACTG 5097s, found that clearance of efavirenz from the body was increased by 32% in non-Hispanic whites compared to blacks or Hispanics. She found a slight association between higher blood levels of efavirenz and study discontinuations, although these did not seem to relate to the incidence of CNS toxicity or to virologic response. An analysis of discontinuations by race/ethnicity was not performed. No association with gender was observed.

David Haas, of Vanderbilt University in Nashville, presented a genetic analysis of a subset of 89 individuals from the A5097s study. Haas found that a single nucleotide polymorphism (SNP) that changed the DNA code from a "G" to a "T" at position 516 of the gene for the CYP2B6 metabolic enzyme was associated with slower clearance of efavirenz, higher blood levels of the drug and more CNS-related side effects.

Median AUC (a measure of total drug exposure) of efavirenz levels was about 3 times higher with the CYP2B6 position 516 TT allele than with GG. But after controlling for these alleles, there was no association between race/ethnicity and efavirenz levels. The TT and GT alleles were also significantly associated with a greater number of CNS-related adverse events at the initiation of therapy, which gradually disappeared by 24 weeks, even though higher efavirenz levels persisted. However, there was no association with viral load response.

Overall, in the study and in a separate representative population sample of DNA, at least one G516T allele appeared in 21% of European-Americans and in 38% of African Americans. The double-dose TT allele occurred in about 20% of African-Americans but in only 3% of European Americans. The study also detected a number of SNPs in other metabolic enzymes, but none were as strongly associated with the blood levels of efavirenz. While having the TT allele might be expected to predict better efficacy of efavirenz, it may also contribute to higher discontinuation rates if side effects are more pronounced. Both of these require further analysis.

The CYP2B6 G516T SNP had not previously been recognized as a factor in efavirenz metabolism. This enzyme also metabolizes nevirapine, nicotine, tamoxifen, bupropion, diazepam and Ecstasy, so more study of its impact on individual dosing and the potential for drug-drug interactions should be followed-up. The effect of this polymorphism on nevirapine is most critical, since it is poised to become the most widely used antiretroviral drug in the world. Surveys of the frequency of the G516T allele in worldwide populations should be conducted right away, and analysis of Boehringer's extensive safety database should be done to look for correlations of toxicity with the SNP. Studies should also continue to evaluate if genetic testing for every known SNP affecting drug metabolism can help individualize therapy to avoid toxicity and maximize efficacy.

Ribaudo H, et al. Relationships between efavirenz pharmacokinetics, side effects, drug discontinuation, virologic response, and race: results from ACTG A5095/A5097s. 11th CROI, 2004, Abstract 132.

Haas D, et al. A common CYP2B6 variant is associated with efavirenz pharmacokinetics and central nervous system side effects: AACTG Study NWCS214. 11th CROI, 2004, Abstract 133.

TRIM5, but it is not able to block the virus nearly as efficiently as monkey TRIM5. This new point of interference suggests the possibility of administering a block with a drug or possibly gene therapy. More discoveries like this are almost certainly waiting in the wings.

Budding Genius

Although much recent attention has been given to explaining how HIV binds to and gets into a cell, far less is known about how a newly formed virus leaves a cell. This phase of the viral life cycle is called budding. At the Sunday night plenary that opened the conference, Wesley Sundquist, a virologist at the University of Utah, gave a detailed tour of the mechanism HIV uses to export new virions from an infected cell. First, all of the proteins and RNA that make up a new viral particle must be guided through a briar patch of actin molecules that cluster just below the lipid membrane and give shape and mobility to the cell. Then the premature viral core has to be directed to a site on the membrane that is permissive for virus release. Since HIV is clad in an envelope made up of its host cell's lipid membrane, a new virion has to wrap some of the membrane around itself like a tiny bubble then finally pinch off the last tethering bit before it can go free. Cellular factors are at work in every step of the budding and release process, another example of the body inadvertently helping to send new viruses out into the world.

The FDA has asked the pharmaceutical industry to voluntarily provide information on the pharmacogenetics of their drugs.

Sundquist's group identified a host protein associated with HIV budding called TSG101. Fortunately, this protein had already been studied for its role in a cellular housekeeping process that sends unwanted cell-surface proteins to their destruction in the lysosome, a membrane-enclosed bubble inside the cell filled with digestive enzymes. The obsolete proteins are marked for destruction then conveyed from the cell's surface and inserted into the lipid membrane of the lysosome. But before they can be destroyed they need to be brought inside the bubble. This is done by pinching off bits of the membrane holding the doomed proteins and forming tiny vesicles, which are released to the interior of the lysosome. In this regard, vesicles are very similar to HIV particles, and the mechanism that forms these vesicles is probably the same process that HIV hijacks to engineer its release from the cell. TSG101 is kind of routing ticket that directs a protein to the vesicle formation machinery. HIV seems to use TSG101 to send itself to the outside world instead. The details of how this happens are complex and not fully understood, although, Sundquist said, so far we know of at least 20 host proteins involved, with more likely to be found. (Sundquist's fascinating lecture can be viewed as a webcast at: www.retroconference.org) If HIV inserts itself into this chain of events in some unique way, then a possible treatment might be designed to stop or slow budding without causing havoc to any natural process.

All Over the Map

Variability is not only for genes; it occurs in the scientific literature as well. Telenti took an aside to note the many published discrepancies on the significance of certain host proteins for HIV pathogenesis. P-glycoprotein (P-gp) is a membrane-bound drug transport molecule that protects cells from toxic intruders such as cancer chemotherapies and HIV antiretrovirals by pumping them out of cells. But by lowering the concentrations of protease inhibitors within cells, P-gp can hinder antiviral efficacy. Just as some people produce different amounts of CCR5, some people have different alleles of the MDR1 (for multi-drug resistance) gene that produces P-gp, with different sets of alleles producing greater or lesser amounts of P-gp. A study by Telenti's group published two years ago found an association between different MDR1 alleles and greater rises in CD4 counts within six months of starting an antiretroviral regimen containing nelfinavir or efavirenz. The theory is that people who express less MDR1 have less P-gp, which means that less drug is pumped from their cells and antiviral activity remains higher, longer. (See "The Genetic Edge," *GMHC Treatment Issues*, January 2002.)

But other reports have suggested that P-gp, even in the absence of therapy, might play a role in how permissive cells are to becoming infected with HIV. A few laboratory-based experiments have shown a dramatic decrease in viral replication in cells that produced P-gp abundantly; protection that was lost when P-gp blockers were added. One theory holds that P-gp may be interfering with various lipid molecules on the cell's surface that are needed to assist with HIV fusion and entry. But these reports have been controversial, partly because some of the cells studied expressed over 1,000 times as much P-gp as T-cells do. A new report from Telenti's lab casts doubt on these previous findings with results from an experiment using T-cells with normal levels of P-gp.

T-cells were collected from 128 HIV-negative persons (representing the variety of MDR1 alle-

les in that population). The cells were infected with a laboratory strain of HIV and then characterized for permissiveness to infection. When the MDR1 alleles of the donors were correlated with the results of the permissiveness assay, no association was evident between P-gp levels and a cell's susceptibility to HIV infection. But given that such contributory associations are typically small, will these negative results settle the matter? Or does the fact that multiple reports have come up with multiple conclusions signal that something about the field is not ready for prime time? The stakes are likely to be high.

Genes, Drugs and Money

One day, perhaps, before a person steps across the threshold to initiating antiretroviral therapy, the pharmacogenetic likelihood of their response to various medications may be evaluated. The genes for factors that influence exposure to drugs, such as the cytochrome metabolic proteins, P-gp and other transporters will no doubt be analyzed. Next, the toxicogenetic markers for trouble will be examined to prevent toxic catastrophes. An HLA type associated with abacavir hypersensitivity has been located and soon a simple screening test might simplify the use of this drug. And recently an allele in the cystic fibrosis gene has been associated with susceptibility to pancreatitis, a well-known serious side effect of ddI toxicity.

But even mild toxicity can impact efficacy if intolerability leads to discontinuation or missed doses. It would be helpful to know before a drug is prescribed, who is at risk for having unpleasant reactions and who can be predicted to have only benign side effects. One talk at the conference showed that African-Americans may have higher blood levels of efavirenz than European-Americans. But does that translate into better virologic response or does it mean more dropouts due to CNS toxicity? Additional study is required. Ritonavir-boosted protease inhibitors have become standard-of-care, yet ritonavir elevates triglycerides and cholesterol for too many who take it. Individuals with the apoE gene, found in 27 percent of the population, are likely to have elevated lipids at baseline or a higher risk for developing them. It may become useful to screen for that underlying propensity before initiating treatment.

All of this has caught the attention of the U.S. Food and Drug Administration (FDA), the body responsible for ensuring the safety of drugs in the U.S. In attempting to understand the potential for genetic screenings to make medicines safer, the FDA has asked the pharmaceutical industry to voluntarily provide information on the pharmacogenetics of their drugs and has promised not to be prejudiced by what they learn when it comes to regulatory decisions affecting the companies. Many in the industry are skeptical and worry that this new body of knowledge will slow drug approvals. Yet others see opportunity. By selecting out individuals likely to have adverse events or fail to benefit, clinical trials could become more focused and produce results sooner and with more information on the safe use of the drugs.

It would be helpful to know before a drug is prescribed who is at risk for unpleasant reactions.

Before this can happen, Telenti says, more—and better quality—research must be done. In reviewing published reports of genetic associations, Telenti found that contradictions and equivocal findings are the rule; only 30 percent of them can be considered true. Since the strength of association of individual genes with complex traits tend to be weak, larger study samples, stronger statistical methods and more rigorous study designs are needed. He recommends building larger cohorts and research consortiums, including cohorts in the developing world, with appropriate ethical safeguards. Finally, laboratory scientists need to continue to uncover the biological secrets of genetic determinants so that clinical medicine can make the most of them.

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Bleiber G, May M, Suarez C, et al. MDR1 genetic polymorphism does not modify either cell permissiveness or disease progression before treatment. JID, 15 February, 2004:189;583–586.

Best of the Retrovirus Webcasts

By Bob Huff

Some of the most important talks at the 11th Annual Retrovirus Conference this year are now available as free webcasts. If you did not attend the conference or were unable to catch every session, you can access over 20 hours of plenary talks, mini-lectures and symposiums offered as video and audio accompanied by synchronized slides. A low-speed connection offers voice and slides without the video. As you work your way through these talks you will be exposed to the latest issues in the science and social reality of HIV and AIDS.

Listening to Stephen Lewis is like witnessing a great orator from the 19th Century.

Many of the talks delve deeply into scientific details of their subject and may be incomprehensible to those without some background in the topic. Other talks discuss the science in a clear manner and are worth tackling even if one's scientific literacy is low. A few talks cover issues that everyone should become familiar with, such as the crisis of HIV in the developing world, the state of the epidemic in U.S. prisons and jails, and the potential for developing an effective microbicide. Here is an annotated guide to Retrovirus on the web.

www.retrovirus.org

General Interest

Stephen Lewis

(Sunday, 5:30 PM; Opening Plenary; Click the index button and skip to Lewis' talk)

If you have not heard of Stephen Lewis, or have only read his speeches on the plague in Africa, start here. Listening to him is like witnessing a great orator from the 19th Century. Lewis sounds a clarion call for treatment and action in Africa. He convinces in the language of necessity, compunction and love. This was truly the keynote message for the conference.

Men on the DL

(Tuesday, 12:00 PM; Men on the "Down Low": More Questions than Answers.)

Greg Millet of the CDC discusses the situation of heterosexually-identified black men in the U.S. who have sex with men. He reviews common assumptions about DL men, the history of the term, outlines gaps in the research and makes recommendations for filling those gaps.

HIV Care in Jail

(Tuesday, 12:00 PM; HIV in Jails and Prisons)

Jim McAuley of Chicago's Cook County Jail demonstrates that for many people, jail is the only opportunity they have to access health care services. But the short time spent in jail and the high turnover rate poses limitations to the amount of care that can be delivered.

Psychiatric Issues in Youth

(Monday, 4:00 PM; Symposium on Emerging Long-term Complications)

Sharon Nachman of Stony Brook University in New York discusses what is known and not known about psychiatric disorders in children and adolescents growing up with HIV.

Global HIV / AIDS Issues

(Sunday, 3:00 PM; Symposium: Development in the Global Response to AIDS)

Scaling Up from the Top Down

David Miller of WHO presents a comprehensive, if dry, overview of the challenges of scaling-up treatment, prevention and care efforts to reach millions of people who urgently need them. Many of the issues he discusses are also applicable to the need in the U.S. to reach and treat the large numbers of people with HIV who remain unaware of their status or have not entered care.

Planning Treatment in Uganda

Alex Coutinho of TASO in Uganda discusses the scale-up effort in his country where one million people have already died of AIDS, one million have been orphaned and 25 million need treatment. The goal in Uganda is allow parents to live long enough to raise their children. Coutinho focuses on plans for family-based treatment programs aimed at rural areas. Don't miss the gallery of photos from rural TASO treatment centers at the end of his talk.

Treatment in the Private Sector

Gavin Churchyard gives an interesting and detailed report about the first year of the Anglo American Mining company's program for offering therapy to all HIV-positive employees in their South African operations.

Clinical Science

These presentations start with a general overview of the issue and why it is important before veering into deep waters. But stick with it; the presenters all do a great job of making their points clearly with minimal jargon.

Herpes and HIV

(Wednesday, 10:00 AM; Mini-lecture on Global AIDS)

Connie Celum, of the University of Washington, Seattle, describes the symptoms of HSV-2 infection, its interactions with HIV disease, then reviews what is known about the increased risk for HIV acquisition and transmission. Studies of acyclovir therapy in discordant couples are proposed. Graphic content!

Tuberculosis and HIV

(Wednesday, 8:30 AM; Plenary; Tuberculosis and HIV: Is there a Scientific Basis for Hope?)

Peter Small, of the Bill and Melinda Gates Foundation, gives an overview of TB infection and the history of efforts to vaccinate. He also notes increased interest in the "subtle, ongoing dialog" between the host and the pathogen with a goal of tipping the balance towards the host. His conclusions are worth wading through some dense slides, particularly his recommendation that more cooperation is needed between the TB and HIV research establishments.

Malaria and HIV

(Wednesday, 10:30 AM; Interaction of HIV and Malaria)

Richard Steketee, of the CDC, offers viewers a "Malaria 101" talk, then describes what is known about the interaction between these diseases in the developing world.

Women and HIV:

Microbicides

(Monday, 9:00 AM; Plenary; How close are we to a microbicide?)

Robin Shattuck, of St. George's Hospital in London, details the considerable challenges to developing an effective microbicide. One daunting example is the large quantity of product required for current candidates to be effective in animal models. Yet in the end, with the number of candidates and the emerging commitment of resources, the longer-term outlook is promising.

Mother to Child Transmission

(Monday, 11:45 AM; Mini-lecture: Treatment strategies for preventing MTCT)

Ten years after the first historic report that mother-to-child transmission of HIV could be prevented with AZT, Elaine Abrams, of Harlem Hospital, reviews the progress and the potential for continued roll-out of effective approaches. Particular attention is paid to the emerging challenge of resistance in women and children previously exposed to nevirapine.

Treatment Complications in Women

(Monday, 4:00 PM; Symposium on Long-term Complications of HIV)

Bone loss, lipid changes, and body shape changes associated with antiretroviral drug therapy in women. Multiple speakers.

Deep Science (but worth the effort)

Budding and Release

(Sunday, 5:30 PM; Opening Plenary. Cellular Factors and HIV Budding)

Wesley Sundquist, of the University of Utah, Salt Lake. The details are boggling, but the fact of how HIV subverts normal processes to engineer its escape from cells is stunning.

APOBEC3G

(Tuesday, 9:00 AM; Plenary, DNA Editing and Host Restriction Factors)

Michael Neuberger, of the Medical Research Council, Cambridge, UK, tells the story of the discovery of APOBEC3G, a potent, innate anti-HIV defense.

For more on APOBEC3G, see:

(Tuesday, 4:00 PM; Symposium, Host Restriction Factors)

Multiple speakers

Future Therapy

(Wednesday, 4:00 PM; Symposium, Antiretroviral Therapy)

Warner Greene, of the Gladstone Institute in San Francisco, reviews potential new drug targets emerging from basic research.

Amalio Telenti, of the University of Lausanne, discusses the challenges and potential of using genetics to guide therapeutic choices.

Lisa Demeter, of the University of Rochester, gives a fascinating and important talk on emerging evidence about NRTI drug resistance.

World CAB

Focus on International Drug Pricing

Over the past year and a half, HIV community members from around the globe have begun meeting to discuss how they can advance treatment literacy and increase PLWHA input into decisions by the research, education and care programs that affect them. Community advisory boards (CABs) have long been an important vehicle for representing the needs of people living with HIV to researchers and drug companies in the developed world. In February of 2004, for the first time, a World CAB was convened to allow PLWHAs from the developing world to voice their concerns about drug pricing in their regions to senior-level representatives of the multinational pharmaceutical industry. Twenty-eight individuals from 21 countries met with officials responsible for global pricing policy at Roche, GlaxoSmith Kline, and Boehringer Ingelheim. The following is a digest of two of those meetings.

World CAB was convened to allow PLWHAs from the developing world to voice their concerns to the international pharmaceutical companies.

Hoffman-LaRoche

Christopher Murray, Director of International Pharmaceuticals, Roche, Basel

MURRAY: All of our policies regarding access to our drugs come from Roche headquarters in Basel. I have responsibility for these international issues within the company. The Roche pricing policy for protease inhibitors is that Least Developed Countries (LDC) receive a no-profit price from Roche Basel. Currently, the Roche no-profit price is better than that of generic versions of nelfinavir. Roche also offers a clear pricing policy for direct supplies of Invirase and Viracept on ex-factory sales to low-income and lower-middle-income countries as classified by the World Bank.

SUBHA: What does no-profit mean?

MURRAY: No-profit means no marketing or R&D costs are covered. It only covers what it costs to get the drug into a finished pack; no financing or inventory costs. There are no royalties paid to Pfizer, who owns the patents on nelfinavir. Effectively, the no-profit price includes a contribution from Roche. These prices are for direct sales from Basel. We only quote a price in Swiss francs due to exchange rate fluctuations and zero margin. We don't differentiate between public and private sectors. We don't differentiate between any NGO (non-governmental organization). We will only re-price based on changes in economy of scale or reduction of demand.

GREGG: But many of these lower- and middle-income countries still can't afford your drugs.

MURRAY: You may not like the classifications, but this gives us transparency in how we set our prices. I must be rigid because otherwise we will have to negotiate with every country separately.

STERN: The price jumps from $880 in LDC to nearly $2,900 in lower-middle-income countries. This says a lot about the profit to be gained in those countries.

MURRAY: Our transparency policy is not to negotiate country to country. The prices we have

World CAB Participants Represent!

AUGUSTINE CHELLA, ZAMBIA

Speaking as an African, I think treatment is life. Without treatment there is no life. I'm coming from a society where the impact of HIV is visible. In Zambia, where I'm from, we see 39 years of independence and development eroded because of HIV and AIDS. We see its impact on our economy, its impact on our industry, its impact on our educational sector, where since 1999, my country lost 1,600 teachers and we have only been able to train 1,000 teachers. This is a disaster and the government accepts that we have a crisis before us, but the question is treatment. Is treatment readily available in Zambia? No, it's not. We have set a target to treat 10,000 Zambians by 2006, but up to now only 900 Zambians are on treatment. We have a population of two million people living with HIV and about 600,000 of those need treatment immediately.

SUBHA RAGHAVAN, INDIA

In India we are very proud of our generic drug manufacturers for manufacturing all of the potential regimens—but they don't make them accessible to our own people. We export to the developing world,

World Bank Classification of Economies

The World Bank divides economies on the basis of gross national income (GNI) per capita. Pharmaceutical companies use these classifications to set prices outside of the High Income countries The 2002 divisions are:

Low-Income	Average income under $735 per person per year	64 countries
Lower-Middle-Income	Between $736 and $2,935 per person per year	54 countries
Upper-Middle-Income	Between $2,936 and $9,075 per person per year	34 countries
High-Income	Over $9,075 per person per year	56 countries

today are derived from people in your countries saying exactly how much they need.

GREGG: How did you make the decision on who gets the no-profit price?

MURRAY: Kofi Anan asked the pharmaceutical companies to offer the lowest possible price in the Least Developed Countries, and we did.

LOBNA: Can't you offer the no-profit price in countries not on the LDC list where there is a great need but no resources?

MURRAY: No. We are not going to have the no-profit price for regions other than the LDC countries. The lower and middle income countries still receive a reduced price from the European price. We offer an equitable pricing structure.

MARK: You can't say your prices are equitable even though they are uniform, because people can't afford them. We're saying they are not fair, period.

MURRAY: There are huge variations in income levels within and among developing countries. The classification includes oil-rich states and states with a strong industrial base. High-income, non-OECD countries are classed as developing. They pay the middle price of $2900. Upper-middle-income countries pay the regular price. And all of these countries have different prices in-country depending on distribution costs.

There are additional costs for freight, import duty taxes and distribution to be added. For example, the no-profit price ex-Basel is 90.90 Swiss francs, which becomes 125 Swiss francs in South Africa. That's 38% higher:

Clearing, freight and insurance adds 2.5%
Local packaging and quality control adds 6%
Local warehousing adds 4.5%
Distribution adds 8%

So the local cash price is net plus 21%. Then the government adds a 14% VAT (value added tax), which equals a 38% increase.

LEI: We are puzzled by the huge differential between your prices and generic prices.

MURRAY: The nelfinavir sold in Botswana is the same as sold anywhere else. Our suppliers optimize their existing resources. But there is not a huge difference in price between ours and generic nelfinavir.

GREEN: Would increased volume lower the cost?

MURRAY: You would need substantial volume increases to get small reductions in price.

LEI: Are you looking at options to manufacture in countries where costs are lower?

MURRAY: The manufacturing model is to have the machines running 24-hours a day mak-

through the Clinton Foundation, at a much cheaper price than we give our own. We pay one dollar a day or more whereas we are giving it to the Clinton Foundation for 140 dollars per year. So we have this distinction of manufacturing every drug under this umbrella, yet they are not available at affordable prices to our own.

ROLAKE NWAGWU, NIGERIA

Two years ago we had no ARV access whatsoever. The very few drugs we had were from the big pharmaceutical companies, from Glaxo and Roche, and it was just too expensive. In 1998 I paid about 500 dollars a month for my drugs. And that was unacceptable. Two years ago our government announced the roll out of the ARV program and they said they had drugs for 10,000 adults and 5,000 children in 25 centers. The government is paying. These are generic drugs, mainly from Cipla and Ranbaxy: lamivudine, stavudine and nevirapine as individual drugs. The government buys the drugs for about 30 dollars a month and gives them out for about seven dollars a month. There is a waiting list to get in. When this program started, if you went to the HIV clinic it was like death row. The HIV clinic was next to antenatal, which was noisy because you have pregnant women and women with babies; there's festivity there. Next door was the HIV clinic and it was still, because peo-

ing the same product. Moving the site of production doesn't change the cost.

GREEN: We've heard multinational pharmaceutical companies say that this is our rock bottom price. Then generics come in at 1% of that and the companies say: "Now we can reduce the price."

MURRY: If Ranbaxy can make nelfinavir for $600, then you should buy it from them.

OLIVE: Can those of you here from Africa afford nelfinavir?

"The fact that our drugs are not affordable in some parts of the world is not Roche's responsibility."

MURRY: It is not our job to arrange funding. It's not our role to buy our own products. It's the government's role. In South Africa the problem is political apathy. When the government is only spending $5 to $10 a year per capita on health, the situation is their responsibility, not Roche's.

HANNA: But most of the people who need your drugs are poor, so even if they live in a middle income country, they have no access.

MURRAY: We don't have differential pricing within a country. There are people in rich countries who can not afford the drugs. We will not reduce the price any further.

GERMAN: If you know that the Global Fund will be providing the money for a lower or middle income country, will this change your policy on who can get the no-profit price?

MURRAY: No. We will work within the 3 by 5 plan to increase the volume, but that won't change the no-profit status of the price. It is not possible to negotiate for a better price in the middle income countries. We are willing to be priced out of the market in those countries when generics come in.

SUBHA: Can we discuss lowering the $880 price in least developed countries?

MURRAY: No.

MAURO: The most promising untapped market is in the developing world. Why are you giving up on this market?

MURRAY: There is no profit for us.

SUBHA: I want you to leave us with a different message. You have to give us something to help us get going with your drug.

MURRAY: I can't give you anything more. The fact that our drugs are not affordable in some parts of the world is not Roche's responsibility. I can't give you a warm glow when I leave the room.

Boehringer Ingelheim

Larry Phillips, Director of Marketing, Virology and Infectious Diseases, Boehringer Ingelheim.

PHILLIPS: There's quite a learning curve going on in our company about providing access to our drugs in the developing world. For us, in terms of price reductions, there are two ways to go about it. One way is you can donate drugs, which we don't think is a solution. The other way is to grant voluntary licenses to generic drug makers and create competition in the market. We think the best idea is to have as many people producing nevirapine as possible at the local level. True price reduction will never come from one company; it has to come from competition.

Of course, we have to make sure a company we license has the obligation and the capacity to actually produce the drug. We will then grant a voluntary license, but they have to produce the drug and produce a quality drug.

ple had no hope. A year later it became much better because all those who came in sick could see people who used to be like them who now had so much hope. So people wanted to get on this program. After the quota was filled people were still desperate to get on.

ANASTASIA KAMLYK, BELARUS

Most of the people in my country who need it do not have access to treatment. Most of the countries in my region do not have many of the drugs registered. In most countries in my region, AIDS is not a priority for government. Only in Russia and Ukraine have we seen the Global Fund money. Some other countries don't have that many official cases of AIDS so the pharmaceutical companies aren't interested in them. It is not a huge market.

JAMES KAMAU, KENYA

MSF (Médicins Sans Frontières) are doing treatment and right now they are reaching nearly 1,000 people. They are a fantastic example of how to roll out ARV (antiretrovirals) in a resource-poor setting. They are using the triple therapy combination in a single pill, Triomune. It's working out to be much cheaper but the demand is too great. They have successfully shown that it can work. Compliance is 90 percent, which is fantastic. It's because of the way they

ANASTASIA: Is the generic nevirapine the same as your Viracept?

PHILLIPS: There are some differences between the generics and drugs from the developed world, but those mostly have to do with registration issues and not necessarily with potency.

GREGG: Would you also grant voluntary licenses to middle income countries?

PHILLIPS: Eligibility for our donation program is based on lower and middle income status as classified by the World Bank. But in a country where it is obvious that the people can't afford to pay for their therapy, then we are willing to consider voluntary licenses.

Within the industry, everyone is worried about the diversion of generic drugs back into the markets where they make their money. Everyone is concerned with diversion and reimportation, and if it is handled irresponsibly, it damages the process. We don't think it is an insurmountable problem, though. But I think a lot of local legislation is needed. These people are crooks. Voluntary licensing can't be done without some guarantees in the market.

There are also tricky issues with the FDA about voluntary licenses. One has to do with safety. We have a safety reporting obligation, but we can't make the generic companies report their safety.

GERMAN: Your company is interested in granting voluntary licenses. Which countries have you done that with? Are you also interested in doing technology transfer to those countries so they can learn to make the drugs?

PHILLIPS: Technology transfer varies from company to company. When we deal with Ranbaxy, they already have a version of the drug, so it's no problem. We are in active negotiations in South Africa; we are looking in Eastern Europe; we have licensed the Indian companies; and there is a possibility to find one in Asia and one in South America.

ANASTASIA: In Eastern Europe, I don't believe you can't find a producer in our region.

PHILLIPS: Eastern Europe has not gotten the attention it deserves because the immediate concern was Sub-Saharan Africa. You have to sell the idea of making HIV drugs to generic makers. Some don't want to get into HIV because it is such a hassle.

BEN: If BI's HCV protease inhibitor makes it to market, will you have voluntary licenses in countries with large HCV prevalence like Egypt?

PHILLIPS: People like the voluntary license with nevirapine because it is such an easy drug to make. With other drugs it won't be so easy.

GREEN: What royalties do you expect?

PHILLIPS: MSF calls for 3%, which is what we ask for. We ask the company to put it into local HIV programs as part of the contract. But we can't enforce it. If they don't do it we can't pull the license.

"We think the best idea is to have as many people producing nevirapine as possible at the local level."

DELME: The 3% donation can't be enforced?

PHILLIPS: You could try to enforce it, but I don't know how you could. What if you give a voluntary license and the company doesn't produce the drug—do you take it back?

OLIVE: I'm a suspicious person. What's in it for you? I like what you're saying but how does it translate into something we need?

PHILLIPS: Nothing is in it for us. It's philosophical in a sense: There is both a business and an ethical component to pharma. We have a high standard of health care in the North; but our industry doesn't sell cookies. We want to make a profit and we know health is a human right. You can think of all the reasons for why you can't deal with these problems, or you can try to deal with them. It's the belief of the people on my

do it. Before they start you on drugs you go several times for training. After they give you the medication, they follow-up, and they follow-up on opportunistic infections. Having been in the field, they are able to detect the problems much faster. PWAs are involved in their teams; they are in fact the counselors and the people who follow up. Quite a number of MSF patients become educators.

SVILEN KONOV, BULGARIA

In Bulgaria, the only medications we can use are the originator's products. There are no generics. Unfortunately there is only one center where HIV-positive people are treated and the center has only two doctors. With the money from the Global Fund, the national coordinator on HIV/AIDS claims that the system will be decentralized, but so far we see no measures taken in that direction. Doctors outside of that center have no experience and no real knowledge about treatments. Even a rich person would have a hard time getting special care. If you are knowledgeable you can ask for a better combination, but you can not get anything exceptional.

DELME CUPIDO, NAMIBIA

The Government has taken up the drug donation offer made by Boehringer. They are using brand name drugs at the moment through the donation

team that the industry must take responsibility for what is going on. But the governments have to take responsibility too.

We found you can't just give drug away; you have to go out and market it to governments. Within your ability as a company you have to approach governments, WHO and NGOs. Then you need to get the people in your company behind you and try to make it work.

STERN: In Jamaica, there is no patent on nevirapine and a company called Lasco is distributing Cipla's Triomune at an inflated price.

"We found you can't just give drug away, you have to go out and market it to governments. Then you need to get the people in your company behind you and try to make it work."

PHILLIPS: The problem in Jamaica can best be addressed by competition. Where people are poor, there is no way to make it perfect. The pharmacist adds a markup because he wants to eat too.

ANASTASIA: In Ukraine the price of one package of your drug is 100 Euros, in Belarus it is 280 Euros. What is the difference?

PHILLIPS: It's probably due to the local pharmacies. Whatever the ex-factory price is, you can't be sure what the pharmacy sells it for. All we can do is recommend a price.

SVILEN: In Bulgaria we have registered nevirapine, we have the money to buy it, you have local reps there, but still we have no drug.

PHILLIPS: I don't have an answer for you.

LOBNA: In Egypt, the free nevirapine program works through UNICEF but only two women have used it.

PHILLIPS: You have to market the program and tell them it is available, but I can't force governments to use it. We say, use the MTCT donation sites to build your treatment programs upon, since there is at least minimal infrastructure. We lobby where we can, but the NGOs need to get going too.

AUGUSTINE: You've spoken of a strong presence in South Africa, but we don't seem to see the effect in price reductions in Zambia.

PHILLIPS: We are working in Zambia with the nurses association on education. The problem with the granting of voluntary licenses is to get the companies started. With the tenders, you say, I've got a million dollars, how much drug can you give me for that? Supply and demand regulates prices. Then, some countries don't want you to import; they raises taxes at the border, etc. If they can tell us how much drug they want and when, then I can do more.

AUGUSTINE: What are you doing in very rural areas where the need is great?

PHILLIPS: We've approached WHO to have them make these sites part of 3 by 5. We will give help and assistance to qualified groups but we don't want to tell people what to do.

JAMES: Can you do extended stability studies so we can have extended expiry dates, especially in the African climate?

PHILLIPS: We can look into that.

GREGG: What's the pricing policy in middle income places without generic production?

PHILLIPS: We look at our own processes and try to make it cheaper. We produce our drugs in a different regulatory environment and it costs more. Maybe we can farm out production, but we still have to produce to FDA standards, so it still costs more. Producing to WHO standards produces equivalent therapeutic quality, but it costs less. Viramune is produced in Ohio, which is probably not the cheapest place to make it.

GREGG: So, what is the price in those middle income countries?

PHILLIPS: Sixty cents per day, the same as in the AAI (Accelerating Access Initiative) countries.

programs, which is problematic because I'm not sure now sustainable that is. The Government has said to us the intention is to roll out treatment across the country, to expand it to the 13 regions and at the end of it they are hoping to roll out to something like 55 sites across the country. They are doing a progressive realization type of plan; you get the donation then you are able to treat so many people. We are going to get funds from the Global Fund which can then finance the roll-out to other sites. We are on the cusp of getting treatment for a quite a number of people. When that's going to happen, who knows?

KARYN KAPLAN, THAILAND

Because of the Global Fund grant, the government announced a plan to scale-up from 2,000 to 70,000 by 2005. At a cost of about 30 dollars per month, GPOvir (3-in-1 nevirapine, lamivudine, stavudine) is available for 80 percent of the people who can tolerate it. They are planning comprehensive care centers where a person with HIV coming in will immediately meet and be counseled by another person with HIV. Their entire treatment support will come from another person with HIV and this is a key component of the plan. They are already seeing that adherence is better with support that includes equal involvement of PLWAs.

LOBNA: What are the criteria?

PHILLIPS: It is the World Bank criteria, but lower-middle-income countries also get the AAI price.

LOBNA: In Egypt the problem is availability. There's no market so the companies don't register the drugs. The big distributors don't order them. There's no market for generic makers. We simply need cheaper prices.

PHILLIPS: I don't know about the situation there. Where we've had local BI business units for a long time, they have become very independent. Like a lot of companies, we let the local guys run the local businesses. Getting them to approach HIV from a different standpoint has not been all that easy. In the middle income countries prices are often negotiated on a case-by-case basis.

SUBHA: Can you cite a good example of case-by-case negotiations?

PHILLIPS: The CARICOM (Caribbean Community and Common Market) countries approached us as a group and asked for our lowest price, which is what they got. When you apply for registration in Africa, sometimes you can do it in a block for several countries. It would be good if that process were streamlined for HIV.

STERN: I have your prices from the CARICOM negotiations and from your Central American AAI negotiations. I see big disparities between countries in the daily price of nevirapine. The CARICOM price is 60 cents per day, but in very lower-middle-income countries like Nicaragua and El Salvador, your price is $1.66 a day. These are countries where no generics are registered so they must buy from BI.

PHILLIPS: Those countries are controlled by our business unit in Mexico. The Caribbean is controlled by the Canadian BI office. It is a big internal battle within the company. Any company has a lot of politics; and we have a lot of people who came up through the pharmaceutical industry.

STERN: So, here's my headline: "Mexican BI Executives Triple the Price of Nevirapine for Central American People with AIDS." Is that correct?

PHILLIPS: I don't think that headline reflects the intention.

STERN: The AAI, UNAIDS and Peter Piot asked the companies to negotiate in good faith with the regions, yet I know that Central America is paying 2.7 times as much as the Caribbean countries, even though they have lower socio-economic status. So if Canadian BI and Mexican BI are not controlled by German BI, we need to know about it.

"I know that Central America is paying 2.7 times as much as the Caribbean countries even though they have lower socio-economic status."

SUBHA: Could we hear some solutions on how we could follow up on this?

PHILLIPS: Are these countries eligible for the lowest price, which is 60 cents a day? Yes they are. Can I make that happen? Yes I can. And I will. You can help me make this happen by working locally with the representatives. Just please be certain that the prices you quote are BI ex-factory prices and not distributor or pharmacy prices.

But, yes. I can go to the countries that meet the requirements for 60 cents per day and make that happen.

GREGG: Any country?

PHILLIPS: If any country fits the criteria we can do it.

Participants:

David Ananiashvili, Georgian Plus Group, Georgia
Augustine Chella, NAP+—Network of African People Living with HIV/AIDS, Zambia
Ben Cheng, Forum for Collaborative HIV Research, USA
Lei Chou, ATAC—AIDS Treatment Activist Coalition, USA
Polly Clayden, HIV i-Base, UK
Rachel Cohen, MSF--Médicins Sans Frontières, USA
Simon Collins, HIV i-Base, UK
Delme Cupido, Legal Assistance Centre, AIDS Law Unit, Namibia
John Daye, NAPWA—Australia
Roman Dudnik, AFEW—AIDS Foundation East-West, Russia
Olive Edwards, JN Plus—Jamaican Network of Seropositives, Jamaica
Lobna Ibrahim, PATAM—Pan African Treatment Access Movement, Egypt
Gregg Gonsalves, GMHC—Gay Men's Health Crisis, USA
Chris Green, Spiritia Foundation, Indonesia
Mauro Guarinieri, EATG—European AIDS Treatment Group, Italy
Mark Harrington, TAG—Treatment Action Group, USA
Bob Huff, GMHC—USA
James N Kamau, PATAM—Kenya
Anastasia Kamlyk, Positive Movement Belarus, Belarus
Karyn Kaplan, TTAG—Thai AIDS Treatment Action Group, Thailand
Hanna Khodas, All-Ukrainian Network of PLWH, Ukraine
Svilen Kolev Konov, Plus and Minus' Foundation, Bulgaria
Rolake Nwagwu, Nigerian Treatment Access Movement,, Nigeria
Germán Perfetti, Asociación Líderes en Acción, Colombia
Subhasree Sai Raghavan, SAATHII—Solidarity and Action Against the HIV Infection in India, India
Richard Stern, Agua Buena Human Rights Association, Costa Rica
Paisan Suwannawong, TTAG—Thailand
Vladimir Zhovtyak, All-Ukrainian Network of PLWH, Ukraine

News From the Bench

By Bob Huff

Resistance to RNAi inhibition of HIV

Atze Das and colleagues from the University of Amsterdam reported in the *Journal of Virology* that they had successfully expressed small interfering RNAs (siRNA) targeted to the HIV Nef gene that blocked viral replication in long-term experiments. RNA interference is a recently discovered natural process where short (22 base pair) double strands of RNA can target complementary sequences of messenger RNA and prevent their translation into proteins. Previously, siRNA has been shown to be an effective HIV-inhibitor in short-term assays. But the inhibition of replication is not complete, apparently, since escape mutants were observed to appear after several weeks in culture. The resistant viruses had changes or deletions in the Nef sequence, which could evade control by the experimental siRNA. One way around this problem might be a form of combination therapy, where multiple variants of the anti-Nef siRNA sequence are introduced that would block the common resistant mutations as they emerged.

Das A, et al. Human immunodeficiency virus type 1 escapes from RNA interference-mediated inhibition J. Virol. 2004;78 2601–2605

Assay for Less-Fit Phenotype?

An experimental phenotypic drug-resistance assay could potentially model complex viral properties with much more clinically relevant information than current assays offer, particularly for people with multi-drug resistant virus. Commercially available phenotypic resistance assays evaluate drugs individually but may miss synergies resulting from combinations. A flow cytometry-based assay developed by Haili Zhang and colleagues, from Johns Hopkins University, not only reports susceptibility to complete regimens in a physiologically relevant way, but incorporates a measure of replication capacity. Some drug-resistant mutants are less replication-competent than wild-type HIV and certain "salvage" patients may benefit from remaining on therapy despite virologic failure. The assay would allow clinicians to identify which drugs in the regimen were selecting the "less fit" virus, and allow them to stop non-contributing drugs. The assay could also report if a drug combination had residual virologic effect despite the apparent lack of activity by its components.

Zhang H, et al. Novel single-cell-level phenotypic assay for residual drug susceptibility and reduced replication capacity of drug-resistant human immunodeficiency virus type 1. JVirol, Feb 2004, 1718–1729.

Doctors Organize to Protest Abbott's Norvir Price Hike

The annual Retrovirus Conference, the most important scientific meeting of the year on HIV/AIDS, held this year in San Francisco from February 8-13, is not usually an occasion for social or political expression. In fact, the organizers actively discourage demonstrations and leafleting and reward any interruptions with banishment. This year's conference was remarkable for the manifestations of anger and protest at pharmaceutical maker Abbott Laboratories over a 400% increase in the price of their HIV drug, Norvir, announced in December of 2003. Even more remarkable was that the most visible protest leaders were a group of HIV doctors from around the country who have organized a new coalition to speak out about the Abbott outrage as well as on ADAP budget cuts and other threats to their ability to rationally care for people with HIV.

During an afternoon break on the second day of the conference, about 30 physicians representing the newly formed Organization of HIV Healthcare Providers gathered in front of the Moscone West Center and marched two blocks to a press conference at the San Francisco AIDS Foundation where Drs. Bill Powderly, of Saint Louis, Benjamin Young, of Denver, and Edwin DeJesus, of Miami, explained the necessity of resisting the Norvir price hike. Addressing the cameras of CNN and San Francisco news outlets in the packed meeting room, the physicians pledged to boycott Abbott's sales representatives, resign from Abbott advisory boards and refuse to participate in non-essential Abbott research. The Providers have obtained over 200 pledges to support the boycott, said New York physician, Howard Grossman. The press conference was organized by the AIDS Treatment Activists Coalition (ATAC).

Earlier in the week, members of the two large HIV doctor's organizations, the 1,600 member American Academy of HIV Medicine (AAHIVM) and the HIV Medical Association (HIVMA), which had each issued strong letters criticizing the Abbott move, held an unprecedented joint meeting to strategize support for adequate funding for HIV care programs. Members of the new Organization of HIV Healthcare Providers group are planning "white coat" visits to Congress in the coming months to lobby for ADAP and Medicaid funding.

Boosted Reyataz: 48-Week Results

By Bob Huff

Atazanavir (ATV, Reyataz) is the first once-a-day (QD) protease inhibitor (PI) to be marketed in the United States. The drug was approved in mid-2003 at a dose of 400mg QD, to be taken with food. The pivotal studies of atazanavir compared it to the two current standard-of-care drugs for first-line regimens, efavirenz (Sustiva) and ritonavir-boosted lopinavir (Kaletra). Although atazanavir suppressed HIV RNA as well as efavirenz in previously untreated patients in a 48-week trial, it did not perform as well as Kaletra in 24-week data from a comparison of unboosted atazanavir with ritonavir-boosted lopinavir (Kaletra) in treatment-experienced patients. At the time of its consideration by the FDA Antiviral Drugs Advisory Committee shortly before approval, there was concern expressed that low and widely varying trough blood levels of atazanavir may often fail to provide adequate viral suppression, especially in those with pre-existing PI resistance.

To address those worries, the sponsor showed the Committee some preliminary, 24-week data from a comparison of Kaletra with ritonavir-boosted atazanavir (ATV 300mg/RTV 100mg QD) in treatment-experienced individuals with multiple prior protease inhibitor resistance mutations. Although the FDA was not able to review this data for inclusion in the prescribing information, the early data suggested that when atazanavir blood levels were boosted by 100mg of ritonavir, the viral load reductions seen at 24 weeks were equivalent to those produced by Kaletra in this highly treatment-experienced population.

At the 11th Annual Retrovirus Conference, Edwin DeJesus and colleagues have now reported on 48-week data from the comparison of ritonavir-boosted atazanavir with Kaletra (BMS AI424-045). Approximately 120 patients were randomized to each arm of the open-label trial. A third arm offering atazanavir plus saquinavir failed to perform as well as the ritonavir-boosted PIs. The nucleoside backbone was composed of tenofovir (300mg) and one other drug.

The mean reduction in viral load at two weeks was -1.18 log copies/mL for boosted atazanavir and -1.31 log copies/mL for Kaletra. At 48 weeks, the mean viral load reduction was equivalent between the arms, at -1.93 log copies/mL for atazanavir/ritonavir and -1.87 for Kaletra. While the proportion of individuals responding with HIV RNA reductions below 400 log copies/mL was equivalent between the groups at about 57 percent, slightly more persons on Kaletra experienced reductions below 50 copies (46% vs. 38%).

Mean changes in CD4 cell counts were similar in the two groups although the Kaletra group showed a tendency to a greater rise during the first 16 weeks of the trial. At 48 weeks, the mean increase in CD4 cell count was 121 cells/mm^3 in the Kaletra group and 110 cells/mm^3 in the boosted atazanavir group.

Atazanavir (ATV) is distinguished among protease inhibitors by having little impact on blood lipid levels such as cholesterol and triglycerides. Patients in this study who had developed high lipid levels after taking other protease inhibitors experienced normalization of lipids after switching to atazanavir. Lipid levels, especially triglycerides, increased or remained stable in those receiving Kaletra. A dose-limiting side effect of atazanavir may be the development of jaundice or yellowing of the eyes due to bilirubin increases that occur in a large proportion of treated patients. Bilirubin elevations were not associated with hepatotoxicity and did not result in any discontinuations in this trial.

GMHC treatment ISSUES

EDITOR
Bob Huff

ART DIRECTOR
Adam Fredericks

VOLUNTEER SUPPORT STAFF
Edward Friedel

PROOFREADERS
Edward Friedel
Gregg Gonsalves
Richard Teller

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Fax: 212/367-1235
e-mail: ti@gmhc.org
www.gmhc.org

DeJesus E, Grinsztejn B, Rodriguez C, et al. Efficacy and safety of atazanavir (ATV) with ritonavir (RTV) or saquinavir (SQV) vs lopinavir/ritonavir (LPV/RTV) in patients who have experienced virologic failure on multiple HAART regimens: 48-week results from BMS AI424-045. Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8–11, 2004; San Francisco, California. Poster 547.

Fortress NIH

By Gregg Gonsalves

Back in 1992, I co-authored a report about the AIDS research program at the National Institutes of Health (NIH) documenting redundancies and gaps in the effort and the lack of leadership in the program as a whole. Subsequently, Senators Edward Kennedy and Orrin Hatch with Representative Henry Waxman passed a bill substantially re-organizing the AIDS effort at NIH based on our report's recommendations. When the Clinton Administration took office, a new Director of the Office of AIDS Research (OAR) at NIH was appointed. That Director, the eminent immunologist William E. Paul presided over a new era of AIDS research, in which the best scientists in the U.S. and around the world, in consult with community groups, came together to provide strong outside oversight and advice for the nearly billion dollar program.

Paul was a strong force for reform at the NIH but he paid for it dearly—after pushing too hard for change in the NIH vaccine program, the bureaucrats struck back and Paul was pushed from power. However, his successor, noted virologist Neal Nathanson proved no more palatable to the NIH good old boys (and girls) as he continued to seek change. With the ascent of George Bush in 2000, reform came to an end as the scientific leaders of the Clinton years fled back to academia.

The NIH under Bush is notable for its inability to attract senior scientists of the caliber of Paul and Nathanson willing to accept administrative positions. It has also been under siege from conservative ideologues who would like to privatize research or who regularly conduct witch hunts for research on sexual behavior and drug use. The AIDS program at the NIH since 2000 has retreated to the bad-old-days of insular decision-making by second-rate administrators who regularly dole out bad advice, or, like toadies at the court of Louis the XIV, tell their leader, Anthony Fauci, what he wants to hear. Strong countervailing voices of senior scientists like Harold Varmus, David Baltimore, Paul and Nathanson are now generally locked out of decision-making at NIH.

This was clearly evident in the NIH's decision to go ahead with a large phase III trial of two discredited vaccine candidates in Thailand. Despite howls of protest from the best AIDS researchers in the country, NIH has decided to push ahead with the $100 million folly, claiming a duty to the Thai researchers.

The second boondoggle to emerge from NIH over the past few months has been the plan to renew funding for its major AIDS treatment and prevention clinical trials networks, both in the U.S. and in the developing world. In a fleeting moment of courage a few years ago, the NIH arranged for all of the networks' grants and contracts to expire during 2004/2005 so a comprehensive plan could be considered and the entire system reshaped to meet current and future challenges in HIV research. Most of the networks were set up well over a decade ago, and although they've undergone minor changes, their leadership is restricted to a small group of investigators who run the show, each playing musical chairs with the other when their terms on important committees expire.

NIH could have brought in a group of non-network scientists, including experts in newly relevant fields (e.g. hepatitis; TB; operational, outcomes, and health services research; tropical medicine), and a diverse collection of community groups, to offer independent review and analysis and intelligently plot a course for the years ahead. This kind of open, scientific debate on the future of HIV clinical research would have been good for the field and good for the process, but NIH caved in to the political strength of the entrenched network leadership and cut back-room deals with them, reinforcing their power by creating a mega-network with a coordinated leadership structure, putting the good old boys in charge of everything.

So the pendulum has swung. From the reforms of the early 90s, we're now seeing the reaction: NIH has turned inward, neglecting and even spurning the advice of outside scientists and community groups, while relying on its own limited in-house expertise to shuffle around millions of dollars in research money. Such inbred thinking and opaque decision-making is not what AIDS research needs right now. We need greater openness, input and transparency and we need to demand it again, like we did in 1992.