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Agreeing to Disagree: The Future of Microbicides

by Kristen Kresge

For many years, research on topical microbicides for the prevention of HIV has been overshadowed by the development of drugs to treat the virus and its related opportunistic infections. Topical microbicides are creams or gels with active chemical ingredients that are applied in the vagina to block the transmission of HIV during heterosexual sex. The approval process for chemical substances that prevent HIV has not yet been established.

In the US, new drugs must satisfy the Food and Drug Administration's (FDA) stringent requirements before they can reach people in need. Medicines do not hit the nation's medicine cabinets, or even the shelves at the local CVS, without rigorous inspection. For HIV drugs this process has been clearly defined and expedited based on the emergency of the epidemic. Yet various controversies surrounding this process still exist. Now that 19 approved drugs are available, advocates are arguing for both faster and slower approvals for new HIV medications.

But the raging debates over drug approval seem tame when compared with those regarding microbicides, where no approved agent exists. Now that four candidates are nearing or entering the final phase of clinical research where they are tested for efficacy in thousands of people—phase III development—the FDA is being forced to make decisions on what criteria are required for their approval.

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And this decision may not come easily. In late August the FDA brought the issue of microbicide approval before its independent Antiviral Drugs Advisory Committee, the first time that the agency has brought the issue to a public forum. After hours of discussion, many questions lingered, revealing substantial areas of disagreement. The meeting explored issues around the design, size, number, and duration of studies required, and the populations to include in such trials, often with no consensus.

After the limited data from advanced microbicide trials were evaluated and opinions were expressed, the onus fell upon the FDA to articulate a model for bringing a microbicide to market without unnecessary delay, cost, or risk. "I didn't think there was a consensus reached. I did think some interesting ideas were presented and discussed. We're willing to work with sponsors. It's an evolving area and we have to be very flexible. No one has paved the way for the field," said Dr.

Debra Birnkrant, director of the Division of Antiviral Products at the FDA.

“It’s hard, but we recognize the absolute need for these products,” she added. Still the level of disagreement within the FDA advisory panel suggests that the path to approval is largely uncharted.

Urgent Need, Yet Slow Development

Despite a universally recognized need for a prevention method that can be controlled by women without a partner’s consent, the road to developing an effective microbicide has been long and arduous. “I really feel badly,” said Birnkrant. “I’ve been working in this field for more than 10 years and it’s not progressing very quickly.”

Dogging microbicide development from the start has been a lack of funding from the big pharmaceutical companies that bring HIV drugs to market. Viewed as an unprofitable venture, most companies ignored microbicide research, delegating it to government, privately funded organizations, and smaller biotechnology companies.

In these arenas, however, a strong commitment to microbicides exists. Earlier this year, the Bill and Melinda Gates Foundation donated \$60 million to accelerate the discovery of an effective microbicide, acknowledging that women at high risk for acquiring HIV—including commercial sex workers—are unable to negotiate with their partners to use condoms consistently in many areas of the world.

In addition to sex workers, married and monogamous women make up a growing population of HIV-infected women, according to Lori Heise, director of the Global Campaign for Microbicides, a microbicide policy and advocacy group. Studies find that condom use with casual partners is reportedly higher than with regular partners, says Heise, likely because married women are trying to become pregnant and therefore choose not to use condoms. For this reason, microbicides that block transmission of the virus but do not act as a contraceptive are especially attractive.

Also, many women in monogamous relationships put themselves at risk, not only for HIV but also for physical violence, if they ask that their male partners use condoms. This request could be misconstrued as a woman’s admission of promiscuous behavior, which is highly stigmatized in most cultures. Without the ability to use a condom, these women often contract HIV from their male partners who do not know or do not disclose their HIV status. In the US, only 20,000 new HIV infections are attributed to heterosexual sex per

year. In the developing world, there are 16,000 new infections through heterosexual transmission every day.

The majority of these new infections occur in young women. In a single clinic in Hlabisa, South Africa, there was a 51% rate of HIV infection in women between the ages of 20 and 24 in 2001. This has jumped from only 7% in this same age group in 1992.

In light of this ever-expanding epidemic among diverse groups of women, the FDA is now facing pressure to establish just what it will take for a microbicide to come to market. “We need to know that a microbicide, when used, is reducing the risk of HIV. It was very proactive of the FDA to have organized that committee meeting. They now have the opportunity to think about these issues before they’re faced with data,” said Rosalie Dominik, director of Biostatistics at Family Health International, a leading sponsor of microbicide research. The first obstacle they now face is as simple or complex as the control arms in the phase III trials.

Control(s) Freak

Today’s microbicide research is largely influenced by earlier trials with nonoxynol 9 (N-9), a component of spermicides that was evaluated in phase III trials as a vaginal microbicide. In one phase III study with COL-1492 (a version of the N-9 gel), researchers found that N-9 offered no protection against HIV infection amongst female sex workers. In fact there was a significantly lower incidence of HIV in the placebo arm (women who received the vaginal moisturizer Replens instead of N-9) than in the N-9 arm.

This result indicated that N-9 might actually be harmful. Researchers on the study found that the likelihood of becoming HIV infected was twice as high when women developed vaginal lesions, which occurred more often with N-9 use. However in earlier safety studies, the presence of vaginal lesions was the same for N-9 and Replens, and researchers could not rule out the possibility that disruption in the epithelial wall of the vagina was a side effect of a sexually transmitted infection itself. In the end, the study concluded that N-9 not only failed to prevent HIV infection, but was actually harmful. This led to a major reversal in prevention strategies that previously promoted the use of condoms coated with the spermicide N-9.

The problem with using a placebo like Replens is that its effect on HIV transmission—protective, harmful, or neutral—is unknown. A truly inert, or inactive, placebo would ideally have no effect on transmission of HIV. Since the microbicide consists of active chemical

The New Road Map for the Development of HIV Vaccines

by Kristen Kresge

In a landmark paper published in *Science* magazine earlier this year, scientists and policy makers proposed a new strategy to expedite the search for an HIV vaccine. Placing an emphasis on efficiency, the authors of the paper called for all vaccine researchers to coordinate their efforts. This concept is being referred to as the “Enterprise,” after the title of the article: “The Need for a Global HIV Vaccine Enterprise.”

But according to Larry Corey of the HIV Vaccine Trials Network (HVTN) and the University of Washington, the proposed partnership remains unnamed. “I don’t want to use the words ‘road map.’ They don’t seem to work very well,” he said. However, the goal of the effort is clear. The question is, “What is needed to still speed up the process of development?” asked Corey, a co-author of the article.

In the opinion of all twenty-four authors, some necessary steps include standardizing the assessment of both preclinical and clinical vaccine candidates, introducing an international clinical trial system, and developing the resources and facilities required to manufacture a vaccine.

At a recent conference highlighting the development of HIV vaccines, researchers acknowledged perhaps more than ever before the complications and expenses of making an effective vaccine. At AIDS Vaccines 2003, Dr. Anthony Fauci—director of the National Institute of Allergy and Infectious Diseases (NIAID)—delivered a plenary presentation entitled “The Bumpy Road to an HIV Vaccine,” quickly summarizing the current obstacles to vaccine development.

Fauci highlighted the need for a common set of experimental lab standards to evaluate vaccines so that all researchers could learn from the results and compare data from different studies. “Let’s make sure these trials are compatible with each other. You’re going to learn from empirical clinical trials. You may very well learn things to inform future clinical trials,”

said Fauci, another co-author on the article. A trial could prove a vaccine is ineffective and not be a failed trial, and “there is a phenomenally important difference there,” he added.

Fauci also called for increased financial support. He issued an invitation to non-governmental organizations, and to the Bill and Melinda Gates Foundation in particular, to get involved in the Enterprise. Although industry representatives participated in discussions leading up to the Enterprise, none have committed to a definite role in its execution. And Fauci insists that their participation is critical.

“I call upon the other partners that want to join the Enterprise to step up to the plate and bring additional resources. Industry is an absolutely essential partner in the development of a vaccine,” he stated. To inspire industry to participate, Fauci mentioned two major tenets of the Enterprise idea: clinical trial networks and manufacturing capabilities. He suggested that by making an established international network of clinical trial sites available to industry, taking the burden off of companies to develop trial sites, there would be an incentive for them to make their research and results more transparent.

Also by initiating the development of a global manufacturing capacity, for use when an effective vaccine is found, the Enterprise could remove some of the financial pressure from individual corporations. Fauci hopes that by giving industry access to trial sites and manufacturing capabilities, companies might be more willing to share their data with other vaccine researchers. But the pharmaceutical industry seems unconvinced so far.

“It’s a very good concept, but that’s all it is right now. Until the structure actually evolves, it is difficult to visualize,” said Emilio Emini, senior vice president of vaccine research at Merck. But for now he feels that, “there are no *a priori* blocks to industry participating in those endeavors.”

ingredients and carrier agents (ingredients that allow the microbicide to be formulated into a cream or gel), an obvious choice for placebo would be just the carrier agents. Then the placebo would be equivalent to the experimental microbicide and safe, but without any activity against the virus.

However, for various reasons that include the consistency and odor of the gel or cream, developers have

argued that they cannot formulate a placebo that appears indistinguishable from the microbicide under investigation, but contains only the carrier agents. If the placebo looks, smells, or tastes different from the active microbicide, participants in clinical trials would know that they are receiving something different.

Such complications led researchers and regulatory officials to consider adding a second control arm to

future microbicide studies. This arm would be the no-treatment, or condom only arm. Women in this arm would receive neither the microbicide nor the placebo. All trial participants would receive safe sex and condom counseling, but for women in the no-treatment arm this would constitute the only intervention. Adding a no-treatment arm would allow researchers to compare the placebo, as well as the experimental microbicide, with the best preventive method currently available: the condom alone. In theory, the no-treatment arm would reduce the potential to overestimate or underestimate the effectiveness of a microbicide as compared with only placebo.

But addition of a third trial arm introduces a wealth of other complexities. The first obvious difficulty is that you are introducing a third group that is unblinded; participants know they are not getting a microbicide. Those randomly placed in the placebo and microbicide arms will not know which gel they are receiving, but those assigned to receive only condoms will be asked to continue participation in a trial that does not offer them an experimental agent. Keeping participants in this arm will be more challenging. The only previous microbicide study to include a condom-only arm was a trial in Cameroon conducted by Family Health International. This three-arm trial enrolled 1,200 women. Twenty of them were lost to follow-up during the six-month study, and 13 of these were in the no-treatment arm.

Additionally, women who are receiving a microbicide or placebo may share their gel with those in the no-treatment arm, further confounding the results of the study. The success of prevention trials in general depends heavily on the behavior of the volunteers. Aside from sharing gel with those in the no-treatment arm, the results are easily shifted based on other choices made by the volunteers. Relatively small differences across trial arms in the rates of condom use could also drastically swing the results.

In one scenario, the microbicide group might use condoms less frequently because of a potentially false sense of protection, while the no-treatment group could be more adherent to condoms. In this case the microbicide, even if protective against infection, would not look efficacious in comparison with the condom group and could force researchers to abandon the microbicide. Conversely if condoms are used more frequently in the microbicide group, the microbicide would look more efficacious than it actually is, leading researchers to promote use of an ineffective product.

As the hearing demonstrated, these dilemmas in trial design are not easily resolved, and the implemen-

tation of a condom-only arm therefore was the subject of heated and lengthy discussion. Proponents for and against argued vehemently over whether the FDA should require it. Dr. Thomas Fleming, a biostatistician from the University of Washington and principal investigator for the statistical and data management center of the HIV Prevention Trials Network (HPTN), was the most vocal supporter of the condom-only arm, saying that it represented a “real world” analysis of how a microbicide will work.

Others claim that this is not even the question we are trying to answer; rather the goal is just to see if the application of a topical gel could block transmission of HIV. “We want a microbicide that works against the virus,” said Dr. Zena Stein, Professor of Public Health at Columbia University and co-director of the HIV Center for Clinical and Behavioral Studies. “Adding the extra arm is asking a different kind of question. It’s asking if you add a microbicide in the real world would it reduce HIV infection? You can’t do two things at once. It came out at the meeting that proving effectiveness has to come first,” she added. “Time matters in this field. We have many steps to go and proving the concept must come first. We must do it.”

In order to provide this proof of concept, at least one phase III trial is currently scheduled to go forward without a no-treatment group. This study will assess the efficacy of Carraguard, a seaweed-based product capable of killing HIV, being developed by the Population Council. Another phase III trial, which will test the efficacy of a microbicide called Savvy—a detergent-based gel containing the active ingredient C31G—is still in the planning stage. The only trial currently planning to include a no-treatment arm is HPTN 035, a phase IIb study of two active products, BufferGel and PRO2000/5, conducted by Reprotect. BufferGel works by altering the pH in a woman’s vagina, mak-

“We want a microbicide that works against the virus.... Time matters in this field. We have many steps to go and proving the concept must come first.”

ing it difficult for HIV to survive, while PRO2000/5 is an HIV entry inhibitor

Initially the HPTN 035 trial was slated as phase III, but in an attempt to satisfy the FDA's requirements for licensure, the condom-only arm was added. Upon addition of this second control group, the trial was scaled down to phase IIb because of cost. Few organizations are able to afford adding a third arm to a large phase III trial, which is already expensive. The National Institutes of Health, which is sponsoring HPTN 035, would not commit the necessary resources to run a large efficacy trial with as many as 2,000 women per group. "Nobody can afford it. It is very difficult to run these trials. If you add a third arm, you go beyond the inherent difficulties," said Stein.

Running several efficacy trials would involve recruiting several thousand women at clinical trial sites around the world. Adding an additional arm to these trials puts an enormous strain on these sites. "Site capacity isn't even good enough now for two-arm trials," warns Dr. Zeda Rosenberg, chief executive officer of the International Partnership for Microbicides, a group promoting microbicide research and access.

The FDA is sympathetic to the high cost and logistics of running such studies, but the nagging question facing the agency is if the effectiveness of a microbicide can be proven to their satisfaction in a trial without an inert placebo. And with no product already on the market, the FDA is forced to make tough decisions when evaluating microbicide trials. The agency does foresee one possible way to avoid the added cost of the condom arm: the development of a "universal placebo." If an inert substance was tested extensively and found to be safe by the FDA, this placebo could be used in all future microbicide studies and the true effect of the microbicide would be elucidated. Then a condom-only arm would be unnecessary, according to Birnkrant. But a universal placebo would not match the physical characteristics (odor, taste, consistency) of every microbicide and would therefore be easily distinguished from the product being evaluated.

Problems like these were unresolved by the advisory board, which could offer the FDA little in terms of agreement on the third trial arm. "In summary, we're not sure," said Roy Gulick, chair of the Antiviral Drugs Advisory Committee at the conclusion of the discussion.

Recording a Win

Another major point addressed by the committee was just how effective a microbicide must be to be consid-

ered successful. Microbicide trials generally target an efficacy in the range of 33% to 50%. This means that a microbicide would be considered successful if it reduced the rate of HIV transmission by only 33%. By comparison, male condoms, when properly used, are 90% to 95% effective at blocking HIV transmission. The concern has always been that women using condoms will switch to a less effective microbicide, an idea referred to as condom migration.

And if a condom group becomes a mainstay in future microbicide trials, the FDA implied that for approval a microbicide must fare better than both the placebo and the condom. "It would be highly appreciated if it beat the condom as well," said Birnkrant. "Condoms really aren't used that often, however they are the standard of care."

This troubles many microbicide advocates because it sets a very high bar for success. Few expect that any vaginal microbicide will ever be developed that is as effective as a condom. Several committee members repeatedly reminded the FDA that microbicides are urgently needed where condom use is not practical and, in reality, not a standard of care. The irony is that the FDA is making decisions on a product that is desperately needed outside of the US. For now though, it appears that the FDA is more supportive of trials that include a comparison with condoms.

"They decided to make it a requirement, which I don't think it should be," said Rosenberg. "They could end up ruling out a potentially good microbicide."

Yet others fear just the opposite. After the experience with N-9, many are happy to have the US regulatory committee strictly monitor any microbicide trials to prevent a potentially harmful product from becoming widely available to women around the world. For this reason the FDA also heard arguments on whom to include in clinical trials, how many phase III studies to require, and how long participants should be followed after enrolling in a study. On these issues the committee was able to reach some agreement. Most members of the panel suggested including as many types of women in the trials as would use a microbicide if it were approved. This excludes trials that only enroll commercial sex workers or highly sexually active people, who were often favored for testing the safety of a product intended for frequent use. The panel agreed that even casual microbicide users must be part of any trial.

After other arguments over the length of trials, the panel agreed to follow enrollees for as long as practical, but for no less than one year. Most committee members agreed that requiring two years of follow-up was too difficult. Finally, they also concluded that one large

phase III trial that showed a statistically significant efficacy would meet their expectations.

Before any decisions are made though, a microbicide must be successful in preventing infection. “You

first have to find the biological effect, and in the most expeditious way,” said Dominik. “I think that the meeting should help to speed up the approval of microbicides.”

A Mishmash of Data at ICAAC

by Elizabeth Paukstis

If one were to compare the HIV-related research presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) to a film, it would not be a sweeping epic. Instead it would be more like a series of short pieces, with some interesting lines of dialogue and bits of memorable scenery thrown in. As the conference is not exclusively devoted to HIV, no single groundbreaking story emerged, but a few presentations did stand out. Particularly notable studies focused on how old drugs might still be effective for treatment-experienced patients, what the latest data on new drugs showed, whether a once-daily formulation of abacavir could pass muster, and if Kaletra could stand alone in a one-drug regimen.

The Here and Now

Jean-Michel Molina of Pitié Hospital in Paris presented a study examining the use of didanosine (ddI) in a treatment-experienced population (abstract H-447). Upon entering the study, the 168 participants had a median of three thymidine analog mutations (TAMs) and four nucleoside analog mutations (NAMs). In other words, the patients were generally resistant to antiretrovirals from the nucleoside class. Most of them had also taken ddI previously. The volunteers were randomized to add either ddI or placebo to their current regimens. After four weeks, the median viral load drop in the ddI group was 0.6 log, as opposed to a viral load gain of 0.1 log in the placebo group. This difference was statistically significant. The results thus showed that ddI might be effective against resistant virus in people with treatment experience.

However, the study certainly had its limitations. “It provides short-term evidence of the activity of ddI against resistant virus, specifically with AZT mutations,” commented Daniel Kuritzkes, of Brigham and Women’s Hospital in Cambridge. “However, it provides no evidence of whether you can recycle ddI, because the follow-up was too short. It’s uncertain if a ddI mutation might have emerged beyond four weeks. I think the bottom line is that ddI is active in the back-

ground of three TAMs. But how durable this response will be remains to be seen.”

The There and Later

Jacob Lalezari of Quest Clinical Research in San Francisco presented data on T-1249, a fusion inhibitor that has been effective against HIV isolates that are resistant to T-20, or Fuzeon (abstract H-444). Like T-20, T-1249 requires injection, but unlike T-20 it may be injected once rather than twice daily. Fifty-three patients who were failing a T-20 regimen replaced it with T-1249, dosed at 192 mg daily for 10 days, while continuing their background regimen. The median drop in viral load was 1.3 log, and 73% of participants experienced at least a 1.0 log drop. Thirty-four trial participants reported injection site reactions, the painful side effect that also plagues T-20 users. The investigators claimed that these reactions were mostly mild.

While this was promising news for individuals who have developed resistance to T-20, it did not erase the fact that injection is a less than ideal way to take a drug. An entry inhibitor in pill form would be easier to take and render injection site reactions obsolete. Many ICAAC attendees eagerly anticipated new data on Pfizer’s investigational CCR5 inhibitor UK-427,857, a drug administered orally. UK-427,857 interferes with HIV after the virus binds to the cells’ CD4 receptor, but before it binds to the CCR5 receptor. The drug is therefore effective only against HIV that uses the CCR5 receptor, and not HIV that uses the CXCR4 receptor. CXCR4-tropic HIV is generally viewed as a more aggressive form of the virus and is associated with advanced disease progression.

Gerd Fätkenheuer of Köln University in Germany presented results from a trial testing UK-427,857 as short-term monotherapy (abstract H-443). Fätkenheuer began his presentation by stating that preclinical data has shown UK-427,857 to be active against HIV that is resistant to different drug classes. In his study, 24 patients who were prescreened for having CCR5-tropic virus took placebo or UK-

427,857 at 25 mg once daily or 100 mg twice daily. Upon entering the trial, participants had CD4 counts greater than 250 cells/mm³ and viral loads greater than 5,000 copies/mL. By the eleventh day of treatment, people who were taking the 25-mg dose had a mean viral load drop of 0.4 log, while those who were taking the 100-mg dose saw a mean decrease of 1.4 log. The adverse events were described as neither serious nor severe. Pfizer is studying different doses for a phase II trial.

Abacavir as a Once-Daily Drug

Two studies examined regimens that contained a once-daily form of abacavir. The drug's manufacturer, GlaxoSmithKline, is aggressively pursuing this new formulation as a way to enter the popular once-daily market.

Brian Gazzard of Chelsea and Westminster Hospital in London offered detailed results of the ZODIAC study, which compared once-daily administration of abacavir with twice-daily administration of the drug in 770 therapy-naive volunteers (late-breaker abstract H-1722b). The participants had a mean viral load of nearly 80,000 copies/mL; 44% of them had viral loads greater than 100,000 copies/mL. Both groups also took a background regimen containing efavirenz and lamivudine (3TC). After 48 weeks,

66% of people taking once-daily abacavir versus 68% of those taking twice-daily abacavir had viral loads less than 50 copies/mL. Rates of virologic failure were also similar: 10% for the once-daily group and 8% for the twice-daily group. The most common mutations observed in people experiencing virologic failure were M184V (48%), K103N (45%), and L74V (26%). Median gains in CD4 counts were 188 cells/mm³ for the once-daily arm and 200 cells/mm³

for the twice-daily arm. Hypersensitivity reaction, a potentially life-threatening side effect of abacavir, occurred in 9% of the once-daily group and 7% of the twice-daily group.

The investigators concluded that once-daily dosing of abacavir was just as effective as taking the drug twice daily. However, questions arose as to whether the potency of efavirenz, which was used in both trial arms, might have masked any differences between the once-daily and twice-daily formulations of abacavir. It will be important to see how the once-daily form of abacavir fares when used in combination with other drugs.

Another study presented at ICAAC did just that, and produced highly disappointing results. Joel Gallant of Johns Hopkins University in Baltimore presented data on Glaxo-sponsored ESS30009, a trial that compared two once-daily regimens in 345 treatment-naive people (late-breaker abstract H-1722a). Abacavir dosed with 3TC and tenofovir was tested against abacavir dosed with 3TC and efavirenz, and an unplanned interim analysis was performed on the first 194 participants to reach at least eight weeks in the study after numerous investigators reported poor outcomes. Researchers discovered that 49% of the patients in the tenofovir group had viral loads less than 400 copies/mL, as opposed to 90% in the efavirenz group. Forty-nine percent of patients taking tenofovir were classified as virologic non-responders, in comparison with 5% of those taking efavirenz. In addition, the M184V and K65R mutations (indicating resistance to all of the drugs in the regimen) had emerged in most of the tenofovir non-responders.

Based on these dismal results, investigators halted the tenofovir arm and urged that the abacavir, 3TC, and tenofovir combination not be used. Gallant offered several potential reasons for the results, two of which he all but dismissed. The first possibility is that abacavir is not adequate as a once-daily drug, but Gazzard's study would seem to contradict that. The second is that a drug interaction exists between abacavir and tenofovir. However, Gallant pointed to a poster (abstract A-1615), authored by Brian Kearney and sponsored by tenofovir's manufacturer Gilead Sciences, which revealed that tenofovir and abacavir do not alter each other's pharmacokinetics, according to blood level measurements of each drug.

According to Gallant, two other explanations were more plausible. One is that although the drugs do not interact in plasma, they may do so on an intracellular level. This possibility is under investigation. "We can't yet study intracellular levels of tenofovir, but we

"I think it shows that people should prescribe drugs based on clinical trial data, and not because certain drugs seem like they would work well together."

should be able to soon,” Gallant stated. “An assay is being developed by Gilead, but it is not yet available.”

Another hypothesis is that there may have been a low genetic barrier to resistance in this triple-nucleoside regimen. David Margolis, of the University of Texas Southwestern Medical Center at Dallas, explained: “A combination of two mutations affects the activity of all three drugs in the regimen. The K65R mutation confers resistance to tenofovir and is also selected by abacavir. M184V confers resistance to 3TC, is selected by abacavir, and also impacts tenofovir.” So once the virus became resistant to one of the drugs, it also became resistant to the other two. This translated into a weak antiviral regimen.

Whatever the reason, Gallant promised that the issue would be investigated. What was unmistakable was that many HIV-infected people who had never received treatment had both failed their first regimen and developed resistance to key drugs that will hamper their future therapy options. As a result, some conclude that a smaller pilot study of this combination should have preceded the large trial. As Gallant stressed, “I think it shows that people should prescribe drugs based on clinical trial data, and not because certain drugs seem like they would work well together.”

Monotherapy: Making a Comeback?

Results of another study involving treatment-naïve people appeared on a poster from Joe Gathe of Therapeutic Concepts in Houston (abstract 2608). With the acknowledgment that HAART is both highly toxic and costly, Gathe started 30 patients on therapy with Kaletra at his inner city clinic. Kaletra is a fixed-dose combination of lopinavir and ritonavir. Since it is a single pill and ritonavir merely acts as a boosting agent, it could be considered a single drug. Gathe chose Kaletra because of its potency and because resistance is slow to develop in treatment-naïve patients who take the drug.

The mean viral load of 30 volunteers at the start of the study was 262,020 copies/mL. After 24 weeks, 21 people remained, and 70% of them had viral loads less than 400 copies/mL.

Though initially impressive that a single drug could produce such a result, the concept was not universally applauded. “I think a lot of people were terrified by it, too,” remarked Margolis. “And if you look at the whole picture, there were a lot of drop-outs.” Indeed, nine patients—almost a third—abandoned the trial, for the following reported reasons: lost to follow-

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up (2), gastrointestinal intolerance (2), deportation (1), non-adherence (1), virologic failure (1), hepatitis B infection requiring the addition of tenofovir and 3TC (1), and virologic non-response requiring the addition of saquinavir (1).

The trial was also limited in that it did not enroll a comparative arm; a triple-drug arm might have yielded results that would have cast the Kaletra-only arm in a more unflattering light. Margolis also pointed out that a time span of 24 weeks was too short to draw any definitive conclusions. The investigators plan to extend the trial to 48 weeks.

So while this conference did not feature any stunning surprises or breakthroughs, it certainly provided attendees with plenty of food for thought until the next big HIV conference.