

May 2003

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AIDS RESEARCH

The amfAR Treatment Insider

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The Price of Resistance

by David Gildea

Michel Foucault once said, “There are no relations of power without resistance.” Today, the same could be said about the relationship between HIV and the forces that try to suppress it, be they natural immune responses or drug therapy. The Conference on Retroviruses and Opportunistic Infections held in Boston on February 10 to 14 marked a decade of these annual overviews of the latest in HIV research. After ten conferences, researchers keep returning to the same issue: whatever we throw at HIV, this simple, but highly mutable virus finds a way to dodge it.

John Coffin, Director of the HIV Drug Resistance Program at the National Cancer Institute and a professor at Tufts University School of Medicine, started off the conference by declaring, “If you don’t get resistance, the drug is no good.”

That dictum was borne out even in the case of new drug classes, which promise effective salvage therapy for those with growing resistance to the current standard treatments — drugs that inhibit HIV’s reverse transcriptase and protease enzymes.

For nearly the entire past decade, researchers searched for ways to create suitable integrase inhibitors. These drugs would add a major new line of attack by stopping HIV from inserting its genes into the cell’s own genome. Both Merck and GlaxoSmithKline at last have integrase inhibitors in human trials, but they have the resistance issues that parallel those of the standard drugs, according to Daria Hazuda, who directed the Merck integrase inhibitor drug discovery program.

Hazuda described a series of viral culture experiments that attempted to breed integrase inhibitor-resistant HIV. Researchers found a number of mutations that appear in the HIV integrase enzyme after exposure to the Merck, Glaxo and other anti-integrase compounds. Although the Merck and Glaxo products differ structurally, several common resistance-conferring mutations appeared. These mutations occur with other integrase inhibitors as well. This raises the possibility that HIV can become cross-resistant to the integrase inhibitors under development.

T-20 (Fuzeon, enfuvirtide) is a new drug from Roche and Trimeris that blocks HIV entry into uninfected cells. At the *Treatment Insider's* press time, T-20's FDA approval was expected momentarily. As the first agent to attack HIV outside the cell, T-20 should have no resistance problems, at least initially. Alas, that honeymoon is all too brief. Michael Greenberg, Director of Molecular Biology at Trimeris, gave a presentation in which he charted the evolution of HIV resistance to T-20. Greenberg and his colleagues analyzed the genetic makeup of the HIV in 661 participants in phase III T-20 trials, all of whom had a long history of treatment failure before starting T-20 plus an optimized background regimen. Within 24 weeks on T-20, 301 of these participants had again experienced treatment failure.

Earlier studies in this trial cohort found that the likelihood of treatment failure inversely correlated with the number of truly active drugs that supported T-20 in the salvage regimen. When doing genetic analyses on participants' HIV, Greenberg and his colleagues found mutations in a nine-unit sequence in the gp41 envelope protein to which T-20 binds. A single mutation in that region could result in up to 249-fold resistance.

The HIV in some of these trial participants turned out to have as much as 21-fold T-20 resistance even before the trial began. This initial resistance is associated with how HIV attaches itself to cell membranes, reported Eric Hunter of the University of Alabama. That is a sobering thought, since more rapid attachment may lead to a more virulent as well as more resistant virus.

Resistance promotes counter-resistance, as that ultimate dialectician Karl Marx might have said. Many of the new drugs described at the conference are designed to remain active against HIV impervious to present agents. Among these was a new integrase inhibitor from the Rega Institute in Leuven, Belgium. Belonging to a new structural class, V-165 is at least partially active against the HIV that resists other integrase inhibitors, though this particular molecule may yet turn out to be too toxic for human use.

Also, Roche unveiled the first human results for T-1249, a successor to T-20. The trial was a dose-ranging ten-day monotherapy trial in persons who had failed T-20. A median viral load drop of 1.12 logs (92%) occurred. However, the longer that people had been on T-20, the weaker was their response to T-1249.

Many studies at the Retrovirus Conference found that drug resistance paradoxically has some benefits. The mutations that protect against the drugs seem to compromise the ability of HIV to cause disease, at least until compensatory mutations restore viral virulence.

The PLATO collaboration, which pooled 13 observational cohorts, found that persons on therapy could tolerate viral loads of up to 10,000 copies/mL (or up to 10% of their pretreatment viral load setpoints) without declines in CD4 counts. Moreover, the rate of CD4 loss at any particular viral load was higher in treated than untreated patients.

Duke University investigators presented a partial explanation for this observation from their study of patients with "discordant" responses — patients under treatment who had had measurable viral loads but normal CD4 counts for a number of years. If such persons were taking protease inhibitors, their HIV had a highly impaired capacity to replicate. But this impairment was not as apparent in discordant patients taking NNRTIs (efavirenz or nevirapine) instead of protease inhibitors. Discordant responders also had a decreased level of immune cell activation compared with outright treatment failures. This is another sign of reduced viral virulence.

At the end of the conference, Steve Deeks of the University of California at San Francisco described how he tried to take advantage of this reduced replication capacity through "partial treatment interruptions." He followed 20 patients with low, stable viral loads during treatment (median viral load of around 10,000 copies/mL) who stopped either their protease inhibitor or their nucleoside analogs, but not both.

The five that stopped their nucleoside analogs experienced an immediate three- to tenfold increase in their viral loads, whereas the 15 who went off protease inhibitors were stable for 16 weeks. Two of these latter patients have had viral breakthroughs around week 24, though. In these two, viral load rebound occurred as a strain of HIV appeared that lacked the protease inhibitor resistance mutations and possessed improved replication capacity.

Deeks' results indicate that the residual potency of the nucleoside analogs is mainly responsible for the good results in discordant responders with drug-resistant HIV. They may stop their protease inhibitors for a while and experience improvements in quality of life and blood lipids. But the two people in the nucleoside analog arm who now have rebounding viral loads indicate that once again, HIV's evolutionary abilities can overcome any quick fix.

Treatment Interruptions Retain Their Appeal

by Gretchen Schmelz Armstrong

Structured treatment interruptions — in which patients cycle on and off therapy for days, weeks or months — once again occupied center stage at the 10th Conference on Retroviruses and Opportunistic Infections. Attendees heard reports from more than a dozen STI studies in chronically infected individuals. The 48-week results offer tantalizing clues to the perfect drug vacation schedule, which would minimize drug toxicities without undue penalties in terms of CD4 count decline, viral load rebound, or increased HIV drug resistance. At the same time, little now remains of the original hope that HIV replication during STIs could wean patients off therapy forever by provoking effective antiviral therapy.

CD4-Guided Strategies: A New Wrinkle

Jintanat Ananworanich (Thai Red Cross AIDS Research Center, Bangkok) presented data from the prospective HIV-NAT 001.4 study. The 74 heavily treatment-experienced patients had spent a year on suboptimal dual nucleoside analog therapy followed by three years on a protease inhibitor-based regimen. Upon entering the study, they had viral loads of less than 50 copies/mL and CD4 counts above 350 cells/mm³. Participants were randomized to one of three arms. The “continuous” arm received ritonavir-enhanced saquinavir plus two nucleoside analogs without interruption. In the “CD4-guided” arm, study participants began therapy when their CD4 counts dipped below 350 cells/mm³ (or 30% below their baseline count). Those in the “one-week on, one-week off” arm stopped and started treatment every seven days, regardless of CD4 counts or viral load.

No one experienced disease progression, and the percentage of those with CD4 count above 350 cells/mm³ was similar in the continuous and week-on, week-off arms (100% vs. 96%, respectively). Those in the CD4-guided arm experienced an average 178 cells/mm³ drop in CD4 count, with 87% still having a CD4 count above 350 cells/mm³.

Despite the overall figures, serious problems did arise in the week-on, week-off arm. Eight of the 26 failed treatment, defined as a viral load above 1,000 copies/mL (in seven of the eight) or, in one case, a CD4 count below 350 cells/mm³. This arm was cancelled as a result, and everyone in the group resumed therapy. Although all were able to suppress viral load within three months, resistant virus had emerged in some patients.

A Spanish STI study also examined intermittent CD4-guided therapy versus continuous treatment. Lidia Ruiz (Fundació Irsi Caxia, Barcelona) presented this research.

The 122 chronically infected volunteers had good virus suppression (less than 80 copies/mL for at least a year and CD4 counts above 500 cells/mm³ for six months or more). People assigned to the CD4-guided arm could restart therapy if their viral load increased to above 100,000 copies/mL; their CD4 count dropped below 350 cells/mm³; or an opportunistic infection appeared. They stopped therapy if their CD4 count climbed above 500 cells/mm³ and viral loads decreased to below 80 copies/mL.

The baseline CD4 counts were about 825 cells/mm³ at the start of the study. Forty-eight weeks later, CD4 counts remained stable and viral loads undetectable in all but two volunteers on continuous therapy. In the CD4- and viral load-guided arm, 35 of 59 volunteers (57%) had to restart their medication. Participants in this arm lost, on average, 96 CD4 cells/mm³ each month. Twenty-six volunteers (43%) were able to remain off therapy the full 48 weeks, although their CD4 counts decreased by an average 335 cells/mm³ (their average viral load was about 13,000 copies/mL). One side effect that occurred in 6 people (10%) in the CD4- and viral load-guided arm was a flulike acute retroviral syndrome, similar to what occurs when first contracting HIV.

Resistance is Always a Formidable Risk

Although the investigators of the Spanish study did not document resistance, this is always a possibility when virus rebounds. Resistance data was the focus of the early safety analysis of PART, a 273-person study that assigned volunteers to either a continuous treatment arm or an intermittent arm. Stefano Vella (Istituto Superiore di Sanita, Rome) presented the results of the first three of the planned five cycles. During this time, most people (89% in the continuous arm and 97% in the intermittent arm) suppressed virus below 400 copies/mL. When the investigators looked for resistance in these patients after three cycles, they found that 24% had at least one resistant mutation. Half of these persons had at least one mutation when they entered the study. The investigators also noticed that when the STI arm was divided based on the presence or absence of mutations, there was a trend toward a slightly lower response rate to treatment in the group with mutated HIV.

Resistance was the reason a “long cycle” STI study closed early to enrollment. Patients assigned to the intermittent arm stayed off therapy for a month and then went back on for two. The other half was assigned to take treatment continuously. Five people in the intermittent arm developed resistance to protease inhibitors, efavirenz or 3TC.

Moreover, when the investigators looked at 48-week lipid levels, liver function and C-reactive protein (an important marker for heart disease), they could only find a transient decrease in triglycerides at week 40. Mark Dybul (National Institute of Allergy and Infectious Diseases, Bethesda, MD) presented the study. He was not surprised that these levels, which measure drug toxicity, were similar between groups. “If you are on your drugs for two months, your levels are going to increase. We did see a decrease at week 40 [in triglycerides], and one could argue that these transient decreases matter. But what’s disturbing is that the marker for heart disease — C-reactive protein — did not decrease.”

STIs for Deep Salvage

The most controversial aspect of STIs is whether they are an appropriate strategy for people with multi-drug resistant HIV and few treatment options. A treatment interruption in this case might allow for the reemergence of drug-sensitive HIV. But an STI carries health risks from rebounding HIV.

The first was the CPCRA 064 trial, which immediately switched enrollees to a different regimen or waited four months and then switched them. Mean baseline viral load was 100,000 copies/mL, and the mean baseline CD4 count was 180 cells/mm³. The regimens were individually optimized based on resistance testing of a study participant’s HIV. The average number of drugs was 3.8, and in both arms, viral load drops of around 85% were achieved after one month or more of treatment.

This 270-person study stopped recruiting more volunteers because 22 patients in the STI arm either experienced a progression in their HIV disease or died, compared with 12 patients who did so in the continuous-therapy arms.

A much smaller study, led by Christine Katlama (Hôpital Pitié-Salpêtrière, Paris) evaluated 70 people in the GIGHAART ANRS 097 Trial. The investigators randomly

assigned everyone to one of two arms. In the first, patients immediately began a “GIGHAART” regimen (consisting of three to four nucleoside analogs, an NNRTI, hydroxyurea and four protease inhibitors). In the second arm, people began the regimen after a two-month STI. Average baseline CD4 count and viral load were those of advanced AIDS — 27 cells/mm³ and 200,000 copies/mL.

The STI did result in more drug-sensitive HIV. After 12 weeks on treatment, there was a 1.91 log (98.7%) viral load drop in the STI group compared with a 0.37 log (57%) drop in patients on continuous treatment. This effect had diminished considerably after 48 weeks on treatment. The viral load declines from baseline in the STI and continuous arms were, respectively, 0.79 and 0.37 log (84% and 57%). These figures are for everyone in the trial, though at this point only 22% of the continuous therapy group and 47% of the STI group was still receiving GIGHAART regimens. Such a large regimen is very difficult to maintain due to its high toxicity and onerous dosing schedules.

Too Brief an Idyll

“We have some positive data, and some negative data, so we need to study this more,” said Stefano Vella. Much more needs to be ironed out as clinicians search for the perfect STI model. There are obvious setbacks to STIs: drug resistance, acute retroviral syndrome, and CD4 cell loss. But HIV-NAT 001.4 was able to show that volunteers in the CD4-guided arm received therapy for only a third of the time compared with controls for up to one year. “The issue of the STIs is always the long-term effects,” continued Vella. “That’s why we need long-term studies; without them, we have partial results. The follow-up of many trials is always so short. We treat patients for years, not months.” As researchers continue to search for the safest STI strategy, they may be able to fulfill the hope of less toxicity and less cost.

Two Roads Diverged in a Yellow Wood

by Kristen Kresge

This year’s Retrovirus conference introduced a surprisingly robust list of HIV vaccine candidates, both still in the lab or already in human trials. Scott Hammer from Columbia University had the daunting task of providing an overview of the many vaccine trials. Beyond the multitude of trials, Hammer’s talk zeroed in on a crucial obstacle that current vaccine candidates have yet to counter: viral escape.

The Path Less Traveled by...

Most recent vaccine research has focused on establishing cellular immunity, one of the two approaches that the immune system takes in fighting infection. Vaccines aimed at inducing cellular immunity produce killer T-cells in the body, which eliminate HIV-infected cells. This is a new strategy for vaccine development. Vaccines that trigger killer T-cells may not be able to completely prevent

HIV transmission (by producing “sterilizing immunity”), but the immunity they provoke may so suppress viral replication that the infection remains under control with no evident disease. New research indicates that cellular immunity ultimately fails to manage HIV. Viral replication appears over time, and so does disease progression.

Vaccine protection eventually fails because the virus can mutate to become unrecognizable to the immune response, which focuses on a few specific HIV protein sequences. Even while the vaccine-induced immunity is effectively keeping the virus in check, a small amount of HIV replication is still occurring in the cells. This replication is enough to allow the virus to mutate. Once mutated, the virus eludes the immune response mounted by the vaccine and the disease progresses rapidly.

From the start of the conference, studies stressed this viral escape. Dr. Dan Barouch of Harvard Medical School presented results of a monkey experiment that illustrates the ability of the virus to evade a DNA-based vaccine developed by Merck. This vaccine triggers an immune response by inducing cells that take up HIV-derived genetic extracts to provide a mock HIV infection. In this study, four rhesus monkeys were immunized with a simian version of the Merck vaccine and then challenged with a virulent form of simian immunodeficiency virus (SIV). Five control monkeys were given an inactive vaccine. All nine animals were followed over a three-year period.

The four DNA-immunized monkeys showed initial control of virus replication and remained healthy. But eventually three of the four animals lost immune control and became sick or even died. One monkey became sick within the first year after being injected with the virus. Two additional animals experienced an increase in viral replication and became sick after three years of maintaining an undetectable virus level in their blood. The increased viral replication occurred simultaneously with a killer T-cell decline in the animals and the emergence of the same two dominant mutations in the virus.

The slightly mutated virus appeared impervious to the monkey’s immune defense but the vaccine was not a complete failure. The vaccinated monkeys were able to slow disease progression more effectively than the control monkeys. Three of the five control monkeys sickened quickly after exposure to the challenge virus. Another one maintained immune control for at least one year after exposure and then eventually experienced a viral breakthrough. These four animals had the same virus mutations as the three vaccinated monkeys that

became sick, indicating that these mutations are pivotal for viral escape.

One vaccinated monkey and one control monkey are still staving off infection effectively. Although these results are discouraging, Barouch warned against making broad generalizations about cellular immunity-based vaccines. He explained that this study intentionally involved a weak vaccine and a potent virus to more easily detect viral escape.

Barouch strongly cautioned against interpreting these results as the death of the vaccines that elicit cellular immunity. “We’re still very enthusiastic about this approach. The glass is still half full and it still shows tremendous promise,” he said. “This is not a completely negative message.”

Animal experiments utilizing more potent vaccine candidates described at the conference, support Barouch’s comments. John Shiver, Director of Vaccine Research at Merck, offered a latebreaker report on encouraging results from monkey experiments that administered an initial DNA-based vaccine followed by a “booster” comprised of a recombinant virus that enter cells and produces HIV proteins but does not replicate. These prime and boost vaccinations were more effective together than either given alone against two virulent viruses in monkeys. The vaccine plus the boost also provided a 10 to 35-fold reduced viral load compared with control animals up to 136 days after exposure to the test virus.

Merck will present more data on this two-phase vaccine at an April vaccine symposium. In the meantime, research will continue to evaluate the protective effect afforded by cellular immunity-based vaccines.

...Led Us Back to Where We Stood

Despite some encouraging results from both clinical and preclinical vaccine candidates, an obvious paradigm shift in vaccine research took place at the conference. Dr. David Ho, Director of the Aaron Diamond AIDS Research Center and Chair of the Retrovirus Conference’s Scientific Program Committee, declared that recent experiments show the need for researchers to reopen their efforts to develop a different class of vaccines — those that produce antibodies to fight off HIV.

Vaccine research in the early 1990’s took this approach, the traditional one for vaccines, but they quickly ran into difficulties. As opposed to vaccines that rely on killer T-cells, an antibody vaccine would HIV proteins into the body to stimulate the production of

neutralizing antibodies. These would latch onto free HIV in the body, blocking its ability to enter cells while flagging it for destruction.

Work on neutralizing antibodies went out of fashion because the surface of HIV is covered with several sugars. This barrier makes it difficult for antibodies to reach the viral proteins. HIV can easily mutate so that its envelope is impervious to any antibodies that do effectively block it. As a result, promising early antibody vaccines did not prove protective enough. This failure triggered the shift to cellular immunity.

“People said this is going to be hard,” said Dr. Susan Zolla-Pazner, referring to antibody-based vaccines. But Zolla-Pazner, Director of the Immunology Research Laboratory at the Veterans Affairs Medical Center in New York, has been a longtime champion of the need for a vaccine that induces broadly neutralizing antibodies against HIV. Her research has continued to focus on this approach because although cellular immunity may be able to control infection, it never held hope for preventing infection.

Zolla-Pazner’s presentation at the Retrovirus conference concentrated on antibodies that can bind with a section of HIV envelope protein known as the V3 loop. This loop plays an important role in aiding virus entry into cells. Antibodies isolated from HIV-positive indi-

viduals are able to interfere with this part of the viral protein and stop HIV from entering cells. The V3 loop protein can easily change its structure, but the antibodies are able to neutralize HIV with variant V3 loop sequences.

The question then becomes, What substance can serve as a vaccine to evoke such antibodies in the body? Zolla-Pazner called this question reverse immunology. She began her talk with a reference to Johnny Carson’s popular character, Karnac the Magnificent. Much as Karnac already knew the answer but had to come up with the question, researchers like Zolla-Pazner are working backwards.

Neither Zolla-Pazner nor Karnac know what substance could be used to produce such broadly neutralizing antibodies, but they will be working to find out. Zolla-Pazner observed that this is an exciting time for vaccine research because now researchers can focus on rational design of vaccines in the same way that rational drug design produces effective anti-HIV drugs. Her main message about neutralizing antibodies: “Put it back on the table again. It’s important.”

And that seems to be just what is happening. Many researchers “took the cellular fork in the road,” said Zolla-Pazner, but “we’re going to have to have a vaccine that induces both antibodies and a cellular response.”

AIDSVAX: Maybe It Only Works in Chicago

*by David Gilden, with research by Gretchen Schmelz
(and apologies to Chicago native Sam Cooke)*

AIDS fighters’ fondest hope has been that an HIV vaccine will simply and neatly do away with the epidemic, rendering moot all the political and personal barriers to traditional AIDS prevention. They have awaited the results of the first large-scale vaccine efficacy trial with increasing anticipation since the International AIDS Conference last July. At the conference, VaxGen, the vaccine’s developer, announced that its vaccine could be on the market within three years.

The hopes for VaxGen’s AIDSVAX vaccine became more desperate this winter after an early version of the promising Merck HIV vaccine was the subject of a negative report at the 10th Retrovirus Conference (see page 4). Monkeys who received the Merck vaccine were unable to withstand a challenge infection with an HIV-like virus. They first contracted low-level, sub-acute infections but later sickened and died.

The Merck vaccine triggers immune cells to kill HIV-infected cells, but AIDSVAX provokes the production of antibodies to block free-floating HIV. These antibodies may be critical in protecting against initial infection.

Finding a successful antibody-based vaccine faces sizable obstacles because HIV rapidly mutates to protect itself from antibody attack. AIDSVAX is based on only two strains of HIV. More could be added to protect against escape variants, but chasing HIV in this manner threatens to be a Sisyphean task.

Twisting the Data their Way

VaxGen announced its results at a press conference on Monday, February 24. But the twist that the company gave the data left vaccine development as muddled as ever.

Overall, the vaccine seemed to have no protective effect on 5,000 volunteers recruited because of their high risk for

acquiring HIV. About 5.7% of the enrollees in both the vaccine and placebo cohorts became infected with HIV in the course of three years follow-up. “Everyone is very disappointed that we did not see any overall efficacy of the vaccine,” said Susan Buchbinder, an AIDS-VAX investigator who enrolled 150 volunteers at the San Francisco Department of Public Health.

Some 95% of the study volunteers were gay men, most of them white. But a breakdown by race found a surprising difference: Of the 203 blacks who received the vaccine, four (2.0%) became infected compared with 9 of 111 (8.1%) in the placebo group. VaxGen hailed the calculated 78% protection. “This is the first time we have specific numbers to suggest that a vaccine has prevented HIV infection in humans,” said Phillip Berman, VaxGen’s Senior Vice President of Research and Development.

But the more analyses you do, the greater your probability of finding a positive response somewhere. Buchbinder noted, “If indeed the vaccine is efficacious in African-Americans, that would be fantastic. But the study was not designed specifically to get an efficacy answer in different racial groups, and it is possible that the result, while statistically significant, is not ‘real.’ So it is possible that other factors, like trial site, behavior, age, or gender could explain differences between African-Americans receiving vaccine versus placebo.”

Nearly all the apparent benefit to African American occurred because four black Chicago women in the placebo arm acquired HIV. Another odd aspect is that the placebo

and vaccine arms were quite close together until the final months of the trial, when several placebo recipients became infected. Chance variations in safe sex or HIV strain could explain these results.

What a Wonderful Study It Would Be

VaxGen is promising further analyses to prove that some difference in immune response — such as level and type of anti-HIV antibodies — underlies the observed differences in vaccine efficacy. There are no established standards for correlating vaccine protection with antibodies. Persons who produce higher or more potent antibodies after the vaccine might well have been more immune to HIV even before the vaccine. One obvious fact is that African-Americans are not less susceptible to HIV than Americans of European origin. Why then should they respond better to an HIV vaccine?

The company’s emphasis on its very limited dataset from a small nonwhite subgroup is meant to keep its hopes alive (as well as its stock price, which nevertheless fell by over 50% after the trial announcement). VaxGen is playing on the desperate hopes of African-Americans and Africans, too.

A solid demonstration that AIDS-VAX works only in persons of African or African-American descent — or in women — would have required enrolling thousands of such persons. At best, the current trial demonstrates how the lack of HIV research in disadvantaged groups leads to confusion. The worst is that over 5,000 high-risk volunteers are now ineligible for vaccine studies with more hope for success.

Tenofovir Plays Both Sides Now

by Kristen Kresge

Tenofovir, a recently approved drug for treating established HIV infection, may also be a tool for preventing transmission of the virus in the first place. The drug is marketed by Gilead Sciences of Foster City, California under the brand name Viread.

Gilead Sciences announced last May that the National Institutes of Health has embarked on a phase I study to determine the safety and acceptability of tenofovir gel to block vaginal transmission of HIV. Tenofovir’s potential goes beyond such microbicide use to true pre-exposure prophylaxis (PREP).

In October, the Bill & Melinda Gates Foundation agreed to fund a groundbreaking trial on using standard oral tenofovir as an HIV preventive. Family Health International (FHI) of Research Triangle, NC will over-

see this study. By the end of this year, FHI will begin enrolling some 1,600 women from developing countries who are at high risk for sexually acquiring HIV.

Using anti-HIV drugs as prophylaxis is not a new concept, especially in populations where condom use is unreliable. Women employed as sex workers in many African countries have difficulty negotiating condom use with their partners. These women could greatly benefit from a prevention method that they can control. And with effective vaccines remaining unavailable in the near future, new attention has been given to using approved drugs to prevent HIV in adults. “This is a really hot topic and one that looked encouraging,” said Dr. Ward Cates, President of FHI’s Institute for Family Health.

Safety and Convenience

Safety and convenience are the most important factors when choosing a drug for pre-exposure prophylaxis. Any potent drug with a clean safety and toxicity profile and once-daily dosing is appealing — making tenofovir an obvious choice for study. Tenofovir is well tolerated and its overall safety is superior to the older anti-HIV agent nevirapine, which is also under study in PREP. Nevirapine can cause severe, even life-threatening, rashes and liver dysfunction. “As an oral drug it [tenofovir] has a very good safety profile,” said Cates. “It was a wonderful drug to consider.”

Tenofovir is also preferred to nevirapine because HIV very rapidly develops resistance to the latter drug. In contrast, resistance to tenofovir develops relatively slowly. In lab tests, the HIV strains that are resistant to tenofovir tend to be less virulent than nonmutated virus.

Resistance is an important threat in situations where large numbers of people are taking the medication sporadically based on their sexual activities. Intermittent exposure to a drug helps a virus like HIV develop resistance to that drug.

FHI’s PREP study will mainly evaluate primary safety data, including liver, kidney, and bone function. Bone mineral density will be subject to close monitoring because it is the only area where safety issues have arisen with tenofovir. In certain studies, animals receiving tenofovir developed a bone disorder called osteomalacia (calcium depletion). The dose in these studies was much higher than that prescribed for humans, and the condition was treated and reversed completely when drug use was discontinued.

Studies that tested tenofovir’s ability to prevent infection in monkeys, both before and after exposure, have been very encouraging. Cates predicts that tenofovir will have a major impact on prevention in resource-poor countries, where women are often employed as transient sex workers.

Starting Right Off with a Large Trial

All 1,600 participants in the PREP study will be uninfected women who have high-risk occupational sex and a past history of sexually transmitted infections. The four study sites — three in Africa and one in Asia — have yet to be determined.

Female volunteers assigned randomly to the experimental arm of the study will receive a 300 mg tenofovir pill once daily. Those in the control arm will receive a placebo pill, and both active and placebo arms will receive counseling on safe sex and condom use. The study is blinded and will last for one year.

No prior acceptability studies have been done to ascertain if healthy volunteers are willing to take a pill every day or to clarify how tenofovir PREP affects their sexual behavior. These issues will be analyzed during the course of the study, but the main goal is to obtain

information on the safety and tolerability of tenofovir in an uninfected population. FHI is hoping to show that the drug is acceptable, safe, and easily administered.

The organization is enrolling an unusually large cohort for an initial study. It hopes that the extent to which tenofovir protects against HIV will also come out of the study. “Ultimately, the drug could be so effective that we’d be able to show that tenofovir protected versus placebo in this study,” said Cates.

If tenofovir is deemed effective, Gilead will consider providing the drug in those geographic areas where need for prevention is greatest. “There’s a good chance that tenofovir could have an effect in this setting,” said Jim Rooney, Gilead Sciences’ Vice President of Clinical Research. “We would be committed to making the drug available in those areas.”

Gilead last winter announced plans to sell tenofovir at “no profit” to established clinics in 68 poor countries. This program is only for treating HIV, not preventing it.

“In absence of a vaccine, it makes sense to look at other strategies to prevent infection. We’re very excited about this,” said Rooney. But he added: “First we want to answer, does it work?”

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