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A Place in the Sun for Immunosuppressants

by Gunjan Sinha

In 1990, one of Albrecht Ulmer's HIV-positive patients was suffering from recurrent high fever. He tried all sorts of medications to lower it, but nothing helped; his patient could barely get out of bed. In frustration, Ulmer added a common anti-inflammatory drug called prednisone to his antiretroviral drug regimen. The patient quickly improved. This was the general practitioner's first clue that prednisone might help treat people with HIV.

Seven years later, an HIV-positive Rwandan woman walked into Ulmer's large Stuttgart practice complaining of fatigue and depression. "Her CD4 cell count wasn't low enough to start her on antiretroviral therapy," Ulmer recalled. He prescribed prednisone. She, too, began to feel better and her CD4 cell count inched higher. In a few years, the count had nearly doubled.

Since then, Ulmer has prescribed prednisone for over 200 chronically infected HIV patients — those not yet or no longer taking HAART — with varying degrees of success. CD4 cell counts have stabilized or improved in 60% to 70% of his cases. His experience suggests an approach for persons with HIV in the "gray" area of starting treatment — those with viral loads below 30,000 copies/mL and CD4 counts above 300 cells/mm³.

Ulmer's experience does not warrant prescribing immunosuppressants as standard practice to HIV patients. And few in the AIDS research community are even interested in what he has to say. He is a clinician, not a researcher. He has never worked in a lab or published an academic paper. For years he has tried to cap-

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ture the attention of HIV researchers at J.W. Goethe University in Frankfurt — the nearest academic center involved in AIDS research — to no avail. "I would call acquaintances and mention that they should study this. I would get no reply or they would tell me the chief isn't interested," he lamented.

But an emerging body of evidence suggests that drugs that suppress the immune system may have a place in HIV treatment. "There are a lot of good reasons to be looking at the utility of these therapies in selected situations," said Michael Lederman, director of the Center for AIDS Research at Case Western Reserve University in Cleveland.

In fact, Lederman and his colleagues just recruited 40 patients for a trial with another immunosuppressive drug called cyclosporine A (CsA). "We want to look at starting CsA and antiretroviral therapy early, when the [HIV] infection is in a dynamic phase. That is a setting where we are more likely to see an effect," he explained. Other groups are also evaluating CsA during primary infection, including Giuseppe Pantaleo at University of Lausanne in Switzerland and Martin Markowitz at the Aaron Diamond AIDS Research Center in New York.

Immune activation may contribute to disease progression by either driving viral replication or destroying CD4 cells by forcing them to commit suicide (a process called apoptosis). Scientists hypothesize that immuno-

suppressants may quell this active response, potentially tilting the balance between host and virus in a favorable direction.

“It is based on a sound concept, but not a very well digested concept,” commented Robert Gallo, director of the Institute of Human Virology in Baltimore. Since the mid-1980s, researchers have amassed “abundant evidence” in vitro, in monkeys, and in humans suggesting that HIV progresses via indirect mechanisms. But “it takes a long time for that kind of concept to be appreciated in the field,” Gallo continued. By the mid-1990s, several scientists abandoned the question as they witnessed the dramatic effects of antiretroviral therapy in their patients.

Adding to the reluctance is the bad reputation of corticosteroids like prednisone. If taken for long periods, they cause uncomfortable, sometimes nasty side effects like insomnia, weight gain, and diabetes. Prednisone can also cause bone loss over time. The very idea of giving an immunosuppressant drug for an immunocompromising disease is “controversial,” said Jean-Marie Andrieu at Centre Biomédical des Saints-Pères, Université René Descartes in Paris. Since corticosteroids suppress the immune system, people become more susceptible to opportunistic infections — clearly not what clinicians desire for their HIV-positive patients.

Nevertheless, researchers have experimented with higher doses than Ulmer’s 5 mg per day and have reported no serious side effects. In 1995 Andrieu was the first to publish research involving people taking prednisone. For 1 year, he studied 44 patients; some were taking AZT (zidovudine or Retrovir) and other medications. Andrieu reported in the *Journal of Infectious Diseases* (1995;171:523–30) that a daily prednisone dose of 0.5 mg per kg of body weight boosted CD4 cell counts.

Andrieu published a 10-year follow-up of this cohort in May 2004. After the second year, Andrieu continued a prednisone dose of 0.3 mg per kg for only those patients whose CD4 cell counts remained higher than when they entered the trial. And no patient, whether in the prednisone or the control group, took antiretroviral therapy unless their CD4 cell counts dropped below baseline levels.

The proportions of participants who maintained CD4 cells higher than at entry were 43% at 2 years, 11% at 5 years, and 5% at 10 years. Patients whose initial viral loads were less than 30,000 copies/mL maintained significantly higher CD4 cell counts than those whose viral loads were higher. Andrieu observed mild prednisone-related side effects such as darkening of the

skin and weight gain, “but they were not severe,” he said.

In contrast, the proportions of control-group individuals whose CD4 cell counts remained higher than at entry were approximately 12%, 1%, and 0% at 2, 5, and 10 years, respectively.

“This retrospective study obviously does not have the demonstrative strength of a prospective randomized trial,” Andrieu added. He based the control group on medical records of patients treated concurrently at his institution, so they were not as carefully selected as controls in a more rigorous, double-blind, placebo-controlled trial.

Andrieu planned to publish his results after 3 to 5 years of follow-up, “but at that time we were in the story of antiretroviral therapy and the spirit of the clinicians was completely blocked to anything outside of it,” he said.

Mark Milano, a treatment educator at the AIDS Community Research Initiative of America (ACRIA), has taken prednisone for over 10 years and reports none of the nasty side effects associated with high doses. He credits this to a regimen of 15 mg of the hormone every other day. “I have literally no side effects. The critical thing is alternate day dosing,” exhorts Milano, who has lived with HIV for 23 years and managed to remain HAART free. Before switching to alternate day dosing, Milano suffered swelling and joint pain. Now his only complaint is difficulty gaining muscle mass at the gym.

Despite reportedly minimal long-term side effects, researchers are leery of potential harm from prednisone. Only Michael Lederman has published data regarding the drug’s benefit in HIV-infected patients, and he also remains cautious. “Recognize that this approach is unproven. We should only administer [such drugs] in the setting of carefully designed studies,” Lederman cautioned.

In a 2001 study, coauthor Grace McComsey reported that while a prednisone dose of 0.5 mg per kg for 8 weeks was well tolerated, it affected CD4 cell counts only slightly (*AIDS* 2001;15:321–7). But prednisone did lower crucial proteins that signal immune

“It [immunosuppressant therapy] is based on a sound concept, but not a very well digested concept.”

— Robert Gallo

activation. Her team also learned that patients with CD4 cell counts above 200 tolerated the drug better than patients with lower CD4 cell counts — supporting Andrieu’s earlier work.

That study inspired coauthor Robert Wallis to launch another one and publish its results in 2003. For 8 weeks, researchers gave a daily 40-mg dose of prednisone to 24 HIV-infected patients with CD4 cell counts greater than 200 cells/mm³, then a 20-mg daily dose for another 4 weeks. All patients were also taking HAART. After 8 weeks, average CD4 cell counts increased 40% above baseline levels. Side effects included weight gain and elevated cholesterol. But the study ended early when two patients showed signs of osteonecrosis. “Although we were not sure if these abnormalities would progress to clinical disease or were directly caused by the prednisone, we were not prepared to take the risk,” explained Lederman.

Lederman’s group has since scrapped its work with prednisone in favor of CsA because CsA is not a steroid and offers “a more targeted immunosuppressive approach,” he explained. Their ongoing study is similar to Pantaleo’s, which demonstrated that CsA can boost CD4 cell counts when given early in infection and with antiretroviral therapy.

“We wanted to rapidly down-regulate this immune activation to preserve some cells that would otherwise get eliminated,” Pantaleo said. In that pilot study, nine patients took CsA plus antiretroviral therapy and 29 took antiretrovirals alone. At Week 8, all patients stopped taking CsA but maintained antiretroviral treatment. CD4 cell counts spiked in patients taking antiretrovirals and CsA — almost doubling within the first week compared with a historical control group whose counts dropped slightly but not significantly. Plus the CsA group maintained elevated CD4 counts even after stopping CsA — up to 15 months post treatment compared with controls.

“We were a bit surprised by the magnitude of the effect and the rapid recovery of CD4 cell counts,” said Pantaleo. His group hopes to have results from a follow-up study of the same patients soon. Pantaleo is considering supplying CsA for HIV patients during treatment interruptions, periods when they stop taking antiretroviral therapy, to investigate whether the drug can prevent CD4 cell counts from sinking.

“CsA is highly selective for T cells,” Pantaleo explained. “It does not suppress any other type of cell.” And Pantaleo has no plans to study prednisone. “Prednisone has a very broad mechanism [of immunosuppression], which is why using steroids is not a good idea.”

Besides, he continued: “You cannot give prednisone in patients with chronic infection. The toxicity associated with steroids is extremely worrisome. It makes no sense.”

Pantaleo disregards Andrieu’s reports of mild side effects with long-term prednisone. “He used a lot of steroids and, at the same time, he was reporting minimal side effects. That was not credible,” he said. Ulmer counters this by claiming that although the drug is toxic in high doses, the low 5-mg to 7-mg doses he prescribes are therapeutic and cause few side effects.

Over the long term, CsA also causes side effects, so Pantaleo’s group stopped CsA therapy at 8 weeks. “We don’t think that cyclosporine should be given to patients with chronic infection or that it should be administered for a longer time. Just long enough to obtain the results you aim for.”

Despite criticism, Ulmer has plowed ahead. He recently presented his work at an HIV meeting in Toulon, France, as well as at the recent International AIDS Conference in Bangkok. The poster retrospectively compared 60 therapy-naive HIV-positive patients taking a 5-mg daily dose of prednisone with 133 controls. After 3 years, the group taking prednisone showed an average increase in their CD4 cell counts of 127 cells/mm³, while the control group showed an average decrease of 193 cells/mm³. Ulmer also observed that patients who take prednisone during treatment interruptions retain higher CD4 cell counts than those who do not take it.

By Ulmer’s thinking, prednisone could buy HIV patients months, perhaps years, of life free from antiretroviral therapy and its associated toxicities and costs. The drug costs about \$96 a year in the US. And Ulmer’s Rwandan patient? She has been taking prednisone for seven and a half years, is feeling well, and her CD4 count remains stable.

Note: As of summer 2004, no convincing study has been performed that supports the use of any of these or other immunosuppressive agents (such as hydroxyurea or mycophenolate) for the treatment of HIV infection outside of the research setting. This may reflect our lack of understanding of the immune system and how best to evaluate it, the lack of interest from drug companies, patients, and clinicians (for many reasons), the more impressive consistent benefits from potent antiretroviral therapy, or a lack of efficacy. More studies are needed to further elucidate whether fine-tuning the immune system can spare HIV-infected patients from antiretrovirals and/or protect their health in a safe and effective manner. —W. Keith Henry

Weapons of Mass Protection...

by Gunjan Sinha

“Condoms and condom users have been demonized,” over the past several years, said Planned Parenthood’s Susanne Martinez. This is old news to people who have followed the political dogfight playing out in Washington and the media. For example, the Bush administration has proposed doubling the budget for federally supported abstinence-only education programs next year.

Even more alarming, prompted by Congress, the Centers for Disease Control and Prevention (CDC) revamped information on their websites to emphasize condoms’ lack of effectiveness. The site was revised following a review conducted by the National Institutes of Health (NIH) in 2000 that concluded that male condoms are highly effective in preventing HIV transmission, but there was not enough evidence from studies to show that condoms protected against other sexually transmitted diseases such as chlamydia, herpes, and syphilis.

The NIH report clearly stated that a lack of evidence — missing simply because rigorous studies have yet to occur — does not mean ineffectiveness. But these details were lost on the CDC, which chose to minimize condom efficacy and maximize abstinence. “Abstinence and sexual intercourse with one mutually faithful uninfected partner,” the site says, “are the only totally effective prevention strategies.” While no one argues against the veracity of such a statement, groups like Planned Parenthood assert that condoms are unfairly getting a bad rap.

So as government and advocacy groups duke it out, condom manufacturers are hedging their bets on a different strategy to salvage the rubber’s reputation. Selling condoms as defenders against disease was never a completely fruitful tactic anyway, they argue. Manufacturers such as Durex and Trojan are pushing their product with a new mantra: condoms are fun, and psst...they offer protection to boot.

Sales were flat during the 1990s when disease prevention was the marketing mantra, said Richard Kline, vice president of marketing at Trojan. Manufacturers have since decided to focus on enjoyment, introducing a long line of new condom types that promise more pleasure (see opposite page). “Condom usage over the last 10 years has gone up about 25 percent and Trojan volumes have gone up about 60 percent,” said Kline. “So we know that the strategies are producing good trends.”

If trends are any indication, then marketing campaigns may be more helpful in convincing people to use condoms than any information available on government websites or in brochures. While their relatively small sizes and consequent small advertising budgets limit condom companies, both Trojan and Durex do conduct extensive marketing campaigns, often collaborating with other groups that promote sexual health education. They also sponsor events such as National Condom Week. In addition to paid public service announcements on cable television stations such as MTV, Trojan hands out samples of their wares at major party events such as Mardi Gras and Spring Break, where their target audience — 18- to 24-year-olds — gathers.

This crowd of rambunctious and typically irreverent college kids does not pay a lot of attention to the political debates raging in the background. “A lot of people don’t,” said Mark Critchley, group marketing controller at Durex, the largest condom manufacturer in the world. “People don’t like to be preached to.”

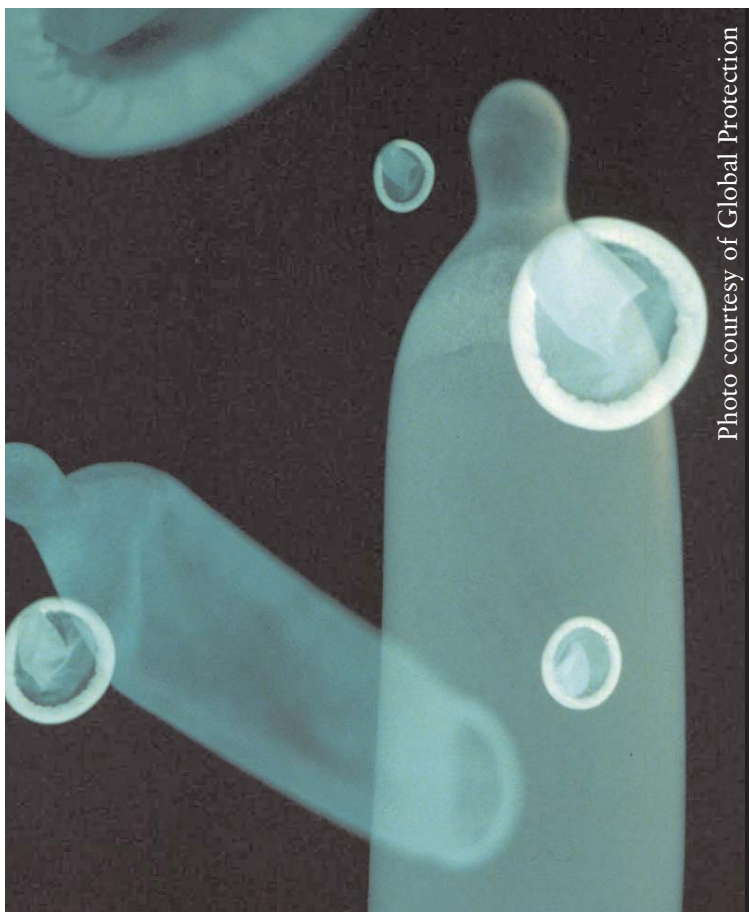


Photo courtesy of Global Protection

Rise and shine: Global Protection boasts the first FDA-approved glow-in-the-dark condom, called Night Light.

That sentiment may extend to the public at large. “We haven’t looked yet at the negative ramifications of government documents that disparage condom use,” said Richard Crosby of the School of Public Health at the University of Kentucky. Crosby provided preliminary data from one state suggesting that residents are highly supportive of condoms and their use, reflecting a disconnect between public opinion and government policy. “Somehow I think all our debate in academic and government circles may be useless,” he remarked. “We don’t know whether or not the American public even looks at these documents. It’s an important question for study.”

The message reaching high schoolers is of greatest concern. There are questions about how to protect the public health of teenagers when sexual education programs are increasingly turning away from teaching about condom use in favor of abstinence only. “Condom manufacturers will not commercially market to young teenagers. But these kids are having unprotected sex,” said Adam Glickman, chief executive offi-

cer of Condomania. “Even public service announcements are not going to reach young kids nearly as effectively as education.”

Meanwhile, new research is restoring the condom’s reputation as a valuable tool in preventing the spread of most sexually transmitted diseases. Based on a review of literature published since the 2000 NIH report, King Holmes printed an analysis in *Public Health Reviews* in June concluding that “condom use is associated with statistically significant protection of men and women against several types of sexually transmitted infections including chlamydial infection, gonorrhea, herpes simplex virus type II, and syphilis.”

Whether or not government information will be updated to reflect this new information is unknown. Ronald Valdiserri, deputy director of the CDC’s National Center for HIV, STD, and TB Prevention, has said that the “CDC routinely reviews, revises, and improves efforts to protect the public health based on scientific updates and information from the field.”

...and Seduction

by Kristen Kresge

From a quirky website animated with a bouncing yellow condom man, Global Protection Corporation peddles sexual protection of the zaniest sort. Glow-in-the-dark condoms, the US’s only patented pleasure condom, and lollipops where candy is substituted with rubber and adorned with smiley faces are among the company’s leading products. Condoms of all colors and flavors are made to look friendly, and even fun. But don’t be fooled: safe sex is the top priority at Global Protection.

Getting people to love latex has been a passion of company founder and president Davin Wedel since his undergraduate days at Tufts University. From there he partnered with classmate Adam Glickman to start the specialty store Condomania. Wedel then became founder and president of Global Protection. His goal was to make condoms as socially acceptable as toothpaste. And according to Wedel, the best way to do this was to focus on the pleasure of condoms rather than dwell on their ability to prevent sexually transmitted diseases like HIV.

“We try to associate the condom with things people like and convince them that condoms can augment their experience. That’s what we were founded on,” said Wedel. This is increasingly important at a time

when many suffer from “condom fatigue.” As he pointed out, “people aren’t afraid anymore, so you need to constantly remind them.”

Global Protection’s top seller is a patented condom that enhances the sexual experience by increasing friction for the penis. Pleasure Plus has a ribbed latex pouch on the end of the condom that adds sensation. Introduced in 1999 as the first condom with “pleasure” in its name, Pleasure Plus is a favorite of the health care community because it inspires people to use condoms more consistently. A study conducted at Emory University found that this condom was preferred eight to one over the best-selling Trojan prophylactic.

But the novelty of the Pleasure Plus condom lies as much in the design of the latex as in the packaging. It resides in a sleek metal tin with rounded edges, rather than the typical cardboard box. The package calls attention to the product when shelved alongside other brands and can be thrown into a briefcase or pocket as easily as a tin of breath mints. “Condoms have always been packaged the same way,” said Wedel. But when partners unwrap a Pleasure Plus, it appears cool and sophisticated. “It’s very sexy,” he remarked. “Very different.”

Another Global Protection product is less about pleasure and more about playfulness. “Rise and Shine”

is the motto of Night Light, the only FDA-approved glow-in-the-dark condom. “Inherently, condoms are taking something away from the sexual experience. This is a condom that adds something,” said an enthusiastic Wedel. “It’s literally making it fun.”

Condomania’s most profitable rubber innovation is the custom-fitted condom. The contraceptive emporium hawks 55 different sizes of condoms on its website and claims they are both safer and more enjoyable. After determining their size with a fitting kit, men can order condoms anywhere from three to ten inches in length. According to Glickman, chief executive officer of Condomania, the launch of custom-fitted condoms was the most successful in the industry. So successful in fact — more than 100,000 sold — that the company is expanding to 95 sizes soon.

Condomania’s niche is in its direct marketing to consumers through its stores and website. Global Protection does not sell directly to consumers. Nongovernmental organizations and health clinics

buy the bulk of its condoms, while retail outlets purchase the remainder.

A visit to the condom aisle at the drugstore proves that all companies are searching for ways to entice customers. Durex, the world’s leading brand, markets choices like Ultimate Feeling, Enhanced Pleasure, and Performax. The Performax, or Extended Pleasure, condom comes with a dab of the anesthetic benzocaine. Introduced to Americans in 2001, this product allegedly controls climax and therefore prolongs sexual performance.

And as condom sales in the US rise, many people predict more creative approaches to making condoms. “The biggest problem with condoms is that people think they don’t feel good. We found that if we provide a condom that feels good, we could get people to use them,” said Richard Kline, vice president of marketing at Trojan. But for those shopping around for safety, Trojan also offers an Extra Strength condom that is advertised as stronger than regular latex.

WHO to ACT Now

by Olivia Weisser

After years of complacency bred widespread resistance to its most accessible treatments, malaria has reappeared on the Western world’s radar screens. When researchers discovered the drug chloroquine in the 1950s, they hailed it as a cheap solution to the disease. For decades it was widely distributed; some nations even added it to salt supplies. Now the parasite is resistant to the drug. According to clinical trials, up to 64% of East Africans taking chloroquine fail their treatment. And the parasite developed similar resistance to second-line regimens.

Last January, a group of clinicians and researchers attacked the World Health Organization (WHO) in response to rising malaria-related death rates. The group accused the WHO of “medical malpractice” for failing to promote newer, pricier medicine and outlined its failure to alter its malaria policy despite prevailing chloroquine resistance (*Lancet* 2004;363:237–40).

But in 2001, the WHO did officially recommend the most potent treatment, called artemisinin-based combination therapy (ACT), as the first-line regimen for malaria in endemic areas. Today, the WHO’s top four recommended treatments for malaria are ACTs. The organization asserts that responsibility for choos-

ing specific drug policies rests with individual countries — not the WHO.

Amir Attaran, the lead author on the editorial, and 13 others argued that African countries fail to adopt newer drugs because donating governments, specifically the US and Great Britain, discourage ACT due to cost. Novartis Pharmaceuticals sells ACT for 90 cents to \$2.40, compared with a mere 10 cents for chloroquine.

The editorial also censured the Global Fund to Fight AIDS, Tuberculosis, and Malaria — the largest financial supporter of ACT — for funding proposals that require using dated drugs. But in May, the WHO and the Global Fund altered their procedures and allowed countries to change their drug policies without reapplying for grants. And due to attention over the editorial, the Global Fund’s Technical Review Panel also changed existing grants to promote ACT. “According to my understanding, the board has endorsed all the recommendations, which is good,” said Allan Schapira, coordinator of malaria policy at the WHO.

Almost 40% of the world’s population is at risk of contracting malaria. The disease occurs in over 100

countries and is endemic to mostly tropical, rural, and marginalized areas. In Africa, about 90% to 100% of the population is at risk, compared with 5% to 15% of those living in Asia and the Americas. A red blood cell infection transmitted by mosquitoes, malaria results from a parasite that lives in blood. While there are four types of parasites, *Plasmodium falciparum* causes most malaria-related deaths in Africa, Asia, and Latin America. Insecticide-treated nets are a simple form of protection from malaria-laden mosquitoes.

People living in endemic areas are repeatedly infected from mosquitoes, and over time develop mechanisms to kill the parasite or prevent it from replicating. Because children have not yet developed this immunity, they are at highest risk for infection and death. Due to their lowered immunity, pregnant women comprise the second highest risk group. Malaria increases the risk of stillbirth and low birth weight. HIV-infected people are also more susceptible to malaria, though few studies exist within the coinfecting population. Some new research presented at the XV International AIDS Conference in Bangkok indicates that coinfecting pregnant women are more likely to transmit HIV to their babies (see “HIV and Malaria: A Malefic Mix”).

Strategies for treating malaria vary depending on factors such as available drugs, the type of malaria, and the parasite’s resistance patterns. The relatively new artemisinin class, a component of ACT, originates from sweet wormwood, a 2,000-year-old traditional Chinese remedy for fever. The plant-based drug is combined with at least one other antimalarial to knock out the parasite. Artemisinins act quickly, while the second drug remains active longer and can destroy remaining parasites.

Artemisinin-based drugs are not approved for treating malaria in the US, since sales would scarcely cover the cost of approval. Only one ACT, the Novartis drug, is available as a single pill. This fixed-dose combination contains lumefantrine and artemether, a syn-

thetic derivative of artemisinin; the WHO preapproved it to treat malaria in developing countries. Other drug combinations in development are several years away from approval.

Now, Where Is the Money?

Despite the victory for Attaran and his colleagues, activists persist in fighting for more money. The move to incorporate ACT into existing grants at the WHO and Global Fund will cost an estimated \$1 billion over the next 5 years. Countries with existing grants will also spend their allocated money more quickly than planned on the newer, costlier medicine.

Still, Schapira remains optimistic: “Increased allocations are going to the Global Fund, and the share going to malaria proposals is higher than before.” In 1998, the Global Fund allotted \$60 million to malaria. This swelled to over \$200 million in 2003. In addition, financing for ACT has flowed from Roll Back Malaria partnerships, United Nations organizations, and nongovernmental organizations such as Médecins Sans Frontières (Doctors Without Borders). Although the Global Fund provides assistance for all three epidemics in its name, Schapira claims that to his knowledge, the malaria epidemic is not diverting money from HIV.

But everyone — disgruntled scientists and Schapira alike — acknowledges that the money required to curb malaria-related mortality is severely lacking. “The money for the Global Fund is far from sufficient to cover the needs,” Schapira admits. “Most of the countries in Africa with the worst artemisinin drug situations are requesting support [for] using ACT,” he added. But available money cannot meet this demand. The WHO estimates that by 2005, the need for ACT will grow from 20 million to as many as 220 million treatments per year. “Right now there is well below 50% coverage for real needs, both in terms of treatment and prevention,” Schapira warned.

HIV and Malaria: A Malefic Mix

by Kristen Kresge

Highly burdened regions for malaria and HIV overlap geographically, yet researchers know little about treating both diseases simultaneously. In Africa, the impact of this coinfection on children and pregnant women — the two high-risk groups for malaria — is of particular concern. Several studies evaluating HIV transmission from coinfecting mothers to their babies have produced

conflicting results. But a recent study concluded that babies of coinfecting mothers are much more likely to contract HIV, regardless of maternal viral loads.

“The two epidemics have a synergistic affect on each other. They both facilitate progression of the other disease,” said Dr. Heena Brahmhatt of Johns Hopkins University. She reported on a study involving

300 Ugandan women in a late-breaker session at the XV International AIDS Conference in Bangkok (abstract LbOrC20).

Because of the synergism between HIV and malaria, women battling coinfection often have higher levels of virus in their blood than women with only HIV. A higher viral load at delivery is the greatest risk factor for mother-to-child transmission of HIV. But Brahmbhatt found that despite disease status, coinfecting mothers had HIV-infected babies more often, suggesting another factor exists. The rates of transmission were 31% in coinfecting women, versus only 8% in mothers with HIV alone.

A possible explanation is the concentration of parasite within the placenta, which may damage the placental barrier and put the baby in contact with more of the mother's blood. This is one of several hypotheses, according to Brahmbhatt.

She and her coauthors recommend that pregnant women in malaria-endemic areas take malaria prophylaxis and antiretrovirals to further reduce their chances of transmitting HIV. "We really need to target women at antenatal clinics for both HIV and malaria," said Brahmbhatt. She also calls for more research on the effects of combining these treatments.

Few studies on the interactions between malaria and HIV drugs exist. One examined the combination of ritonavir and the antimalarial mefloquine. Another study by Andrea Savarino (*J Acquir Immune Defic Syndr* 2004;35:223-32) focused on protease inhibitors and chloroquine. The latter study used animal models but suggested that chloroquine can raise or lower protease inhibitor levels, depending on the antimalarial concentration.

Studies on how antiretrovirals affect the potency of malaria drugs are even more urgent. Fluctuations in protease inhibitor concentrations over a short time should have minimal impact on viral control. Weakening the potency of antimalarials, however, could jeopardize their ability to rid the parasite from the body.

Research is required to answer the complex questions of treating coinfecting people. "This costs money and effort," explained Allan Schapira, coordinator of malaria policy at the WHO. "We need scientists to get proactive and submit proposals."

HIV-positive people traveling to endemic areas need to learn about how to treat and prevent malaria. Only three preventative malaria drugs are currently recommended for people in North America traveling abroad: doxycycline, mefloquine, and atovaquone/proguanil. Still, HIV/malaria coinfection remains a



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minor concern in Western countries, and drug companies are unlikely to fund interaction studies.

In endemic countries, the issue of coinfection is relegated to the shadows in the face of more dire concerns, such as accessing any treatment at all. "Antiretroviral treatment is only now beginning to become widespread in Africa, and so many issues have to be addressed with both HIV and malaria," said Schapira. "You have to do things piece by piece."



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