New Momentum for AIDS Research
The *TREAT Asia Report* Interview: Anthony Fauci, M.D.

Since 1984 Anthony Fauci, M.D., has served as director of the National Institute of Allergy and Infectious Diseases at the U.S. National Institutes of Health, where he oversees an extensive research portfolio aimed at preventing, diagnosing, and treating infectious diseases including HIV/AIDS. Dr. Fauci is also a key advisor to the White House and U.S. Department of Health and Human Services on global AIDS issues. In recognition of his achievements, he was awarded the Presidential Medal of Freedom, America’s highest civilian honor, in 2008.

*TREAT Asia Report.* There have been major developments in HIV prevention research in recent months. What do you think it is going to take to realize the potential of this research and what are the major challenges that stand in our way?

**Dr. Anthony Fauci:** I think we have to look at prevention as an issue that has evolved over several years. From the first day, we suspected we were dealing with a sexually transmitted disease, even long before we identified the virus. We knew that safe sex practices and

Investing in Research to Improve Adolescent HIV Care

Providing effective treatment and care for HIV-positive adolescents can be a challenge for physicians. TREAT Asia is currently supporting three studies that it hopes will inform and improve adolescent HIV treatment and care in Southeast Asia.

**HPV infection risks**
A team of researchers from HIV-NAT/Thai Red Cross AIDS Research Centre in Bangkok has received funding for a second year to study human papillomavirus (HPV) infection—a precursor to continued on page 8.

ACASI study initiation meeting in Chiang Rai, Thailand
We Can’t Stop Now

This has been a year of global budget cutting, planned and real reductions in development aid, and threats to the generic antiretroviral drug pipeline. In the midst of endless debates and urgent protests, however, we have seen how investments in HIV research are paying off.

The HPTN 052 study (pages 4-5) showed how earlier treatment can both improve the health outcomes of people with HIV and prevent infection in their partners. The PREDICT study (page 5) reminded us that children in Asia may not fit the same patterns of disease progression as children in other regions. And we are still trying to respond to last year’s research breakthroughs on intermittent pre-exposure prophylaxis (iPrEX) and vaginal microbicides for women (CAPRISA 004). Public health agencies are scrambling to decide whether and how to incorporate these findings into prevention and treatment guidelines.

In the current funding environment, these results alone may not be enough to convince governments and donors that science still matters. An argument that should resonate with policy makers is one presented by Dr. Anthony Fauci (page 7), “Not only is [investing in HIV science] important in saving lives and preventing infection, but it is also going to save a lot of money in the future.” Cost-effectiveness analyses have proven that implementing HIV interventions today saves human lives and resources tomorrow. If we stop now, we will all have to pay an even higher price.

Annette Sohn, M.D.
New Website Reaches Out to MSM in Thailand

TREAT Asia is a proud co-sponsor of www.adamslove.org, a new non-commercial website providing HIV/AIDS information to men who have sex with men (MSM) in Thailand. An initiative of the Thai Red Cross AIDS Research Centre, Adam’s Love innovatively combines education and entertainment and is the first website of its kind in Southeast Asia.

MSM in Thailand face a high risk of contracting HIV. Two-thirds of Thailand’s 20,000 new HIV infections each year occur in MSM, and studies have shown that up to 29 percent of those receiving HIV testing in Bangkok are HIV-positive. Despite this increased risk, stigma and discrimination often prevent MSM from seeking out care at local clinics. Adam’s Love offers an opportunity for MSM in Thailand to access reliable HIV/AIDS-related information from the privacy of their own homes.

“By supporting this type of effort, I believe that we can reach hidden MSM in a more proactive way than we have in the past,” explained TREAT Asia Director Dr. Annette Sohn.

In addition to basic facts about HIV risk, testing, and treatment, visitors can access expert advice and online counseling while connecting with other MSM and enjoying entertainment features like photography and celebrity interviews. Adam’s Love encourages HIV testing every three months and directs users to local clinics where they can access services.

“We sincerely hope that the Adam’s Love campaign will become part of their lives and help them overcome ignorance, fear, and prejudice,” said Dr. Praphan Phanuphak, Director of the Thai Red Cross AIDS Research Centre. “Further, we hope that they will eventually adopt safer sexual practices and come to receive medical services from the Thai Red Cross Society’s Anonymous Clinic.”

Thanks to a high-profile launch campaign featuring a 30-second commercial created by well-known Thai director Marut Sarovart and a fashion shoot with the first Adam’s Love ambassador Chaiwat “Tob” Thongsang, the website has amassed 800 members in its first few weeks of operation. The website’s creative team is now partnering with amfAR to explore initiating a similar “edutainment” website in Indonesia.

PSN Governing Board members

has been to become an independent organization one day,” explained Midnight Poonkasetwatana, current Interim Coordinator of the Asia Pacific Coalition on Male Sexual Health (APCOM) and former PSN Coordinator at TREAT Asia.

Ultimately, the PSN hopes to serve as a key voice of MSM and TG communities in the Greater Mekong Subregion. Its ambitious goals for the future include building alliances with policymakers, promoting social justice for MSM and TG, and equipping PSN members with the skills necessary to implement effective and context-specific HIV interventions.

“PSN will advocate for policy change and resource mobilization for comprehensive HIV/AIDS and sexual health programs in the region and represent a strong collective voice from the community,” said Kyaw Myint, Co-chair of the PSN Governing Board. “Moreover, PSN will be a main body for capacity building and strengthening information flow between communities in each country and other governments and agencies working on MSM and TG issues.”

As the PSN takes steps toward this goal, it will be assisted by several organizations including APCOM, the Australian Federation of AIDS Organizations, the Coalition of Asia-Pacific Regional Networks on HIV/AIDS (7 Sisters), FHI 360, and the U.S. Agency for International Development.
The Exception to the Rule
Discordant Responses to Antiretroviral Therapy

After starting antiretroviral therapy (ART), HIV in the blood typically falls to undetectable levels, leading to increases in CD4 cells that reflect improvements in the immune system. However, some people do not follow this pattern. Instead, they continue to have low levels of virus despite increases in their CD4 cells, or they have minimal changes in their CD4 levels despite having undetectable virus. These are known as “discordant” responses to ART and have been well described in Western settings.

Researchers studied discordant responses among 1,121 Asian and 1,036 Australian patients within the Asia-Pacific HIV Observational Database (APHOD). After 12 months of ART, 19 percent of patients had undetectable virus but limited improvements in CD4 levels, and 12 percent had good CD4 recovery but low levels of virus. This pattern of discordant response was similar at 24 months after ART.

In comparison to those with a typical pattern of response to ART, the 12 percent of patients who had persistently detectable HIV in their blood also had a significantly higher risk of disease progression (i.e., either death or a new AIDS-defining illness). The 19 percent of patients with poor CD4 responses were more likely to be male, have been diagnosed with AIDS before starting ART, and have used the antiretroviral drug didanosine in their treatment regimen. Overall, patients who started ART when their CD4 levels were higher and had discordant responses to antiretroviral therapy, while the other half delayed until their CD4 levels dropped to 250 cells/mm³ or they developed an AIDS-related illness.

During the study, four of the HIV-negative partners in the early treatment group became infected, compared to 34 partners in the delayed group. After taking the follow-up periods for all of the couples into consideration, this meant that an HIV-negative partner in the early treatment group had about one-tenth the risk of experiencing HIV transmission compared to someone in the delayed treatment group.

The researchers also found that the HIV-positive partners who started treatment early had an almost 40 percent reduction in the number of clinical events (e.g., opportunistic infections) associated with HIV disease progression. This study showed that starting antiretroviral therapy at higher CD4 levels can benefit both the HIV-positive and HIV-negative partner.

When One Partner Is Positive
Early Antiretroviral Therapy Prevents HIV Infection in Discordant Couples

HIV sero-discordance is a term that describes when one sexual partner is HIV-positive while the other partner is HIV-negative. Adding to a growing body of research on the use of HIV treatment for prevention, a large clinical trial called HPTN 052 found that early initiation of antiretroviral therapy (ART) can reduce the risk of HIV transmission in sero-discordant couples.

A total of 1,763 couples from nine countries were enrolled in the study. Ninety-seven percent were heterosexual, 61 percent were between 26 and 40 years old, and 30 percent were from India or Thailand. Half of the HIV-positive partners—all of whom had CD4 levels of 350 to 550 cells/mm³—were immediately started on antiretroviral therapy, while the other half delayed until their CD4 levels dropped to 250 cells/mm³ or they developed an AIDS-related illness.

This study showed that starting antiretroviral therapy at higher CD4 levels can benefit both the HIV-positive and HIV-negative partner.
A clinical trial called PREDICT, conducted in Cambodia and Thailand, has shown that older HIV-positive Asian children with moderately suppressed immune systems may be able to delay starting antiretroviral therapy. Researchers followed 299 children between the ages of one and 12 to compare the health outcomes of those starting treatment at CD4 levels between 15 and 24 percent to those delaying until CD4 levels dropped below 15 percent.

After 144 weeks of follow-up, there was no significant difference between the groups of children in terms of the development of AIDS-defining illnesses or death. Both groups showed similar improvements in their CD4 levels and suppression of their HIV virus after starting antiretroviral therapy. Preliminary screening of the children’s visual and motor development skills also did not show differences. However, starting treatment earlier led to faster growth (i.e., weight, height) and reduced episodes of certain HIV-related diseases (e.g., herpes zoster/shingles).

When interpreting these data, the study investigators pointed out that all children had already survived beyond the age of 12 months, which may be an indication that they were not at risk for the rapid disease progression that is seen in some children. They received CD4 monitoring every three months, allowing healthcare providers to start antiretroviral therapy as soon as CD4 levels fell below the threshold. In addition, only 15 percent of the children were under three years old, making it difficult to make conclusions about those in the younger age range.

Current World Health Organization guidelines advise starting antiretroviral therapy in all infected children under 24 months of age; at CD4 levels below 25 percent (or 750 cells/mm³) in children two to five years old; and at CD4 counts below 350 cells/mm³ in children older than five years. Although the PREDICT study raises the question of how the clinical experiences of children living with HIV in the Asia-Pacific may differ from other settings, these treatment initiation thresholds remain critical targets for regional pediatric HIV programs.
behavior modification were at the core of prevention, but getting people to change their behavior is very difficult to do.

Over the last several years, we have begun to look at prevention not as a one-dimensional issue but rather as a combination of modalities. We had the 076 study of mother-to-child transmission prevention followed by the short version of that study with single dose nevirapine. Over the last few years, we have discovered that male circumcision is extraordinarily effective in preventing acquisition of HIV infection among heterosexual men. And then we had the topical microbicide breakthrough. We now have the PrEP [pre-exposure prophylaxis] study for gay men and the PrEP study for heterosexual couples. And we have the game-changing HPTN 052 study, which has really taken down the boundaries between prevention and treatment by establishing that treatment is prevention. We now have within our armamentarium the tools that, if implemented and adhered to properly, can turn around the dynamics of the global HIV pandemic. That is true even in the absence of a vaccine.

What we really need to do right now is implement these tools. Implementation in an arena of constrained resources, particularly in the developing world, is going to provide a serious challenge. But it is a challenge that we need to rise to and meet.

**TA Report: How do you assess the prospects for vaccine research?**

**Dr. Fauci:** I can tell you that a few years ago, I very conservatively said I was not sure that we would actually be able to develop an HIV vaccine because there was no proof of concept that any product could actually have an impact on acquisition. Then we had the RV 144 trial, which—even though the results were modest at best with only a 31 percent efficacy—I feel represented a proof of concept. So while it is impossible for me to predict when we are going to get a vaccine, I think we can say, not with absolute certainty but with some degree of confidence, that we will ultimately develop a vaccine to prevent acquisition of HIV infection. I certainly am much more optimistic about it now in 2011 than I was five years ago.

**TA Report: Can you tell us in broad strokes about the NIH/NIAID strategy on cure research?**

**Dr. Fauci:** To me the definition of a cure is to have a person be disease-free in the absence of therapy, and this can happen in two ways. The first way is complete eradication of the virus in the body. We clearly do not yet have in our armamentarium of drugs the agents to completely rid the HIV reservoir of any trace of the virus. We have to develop innovative approaches for that. I think pure eradication will be a very difficult task.

The other type of a cure is what I have referred to over the years as a functional cure. You do not necessarily eradicate every vestige of the virus from the body, but you try to develop a situation where you do not have any good targets for the virus to replicate in. Alternatively and probably with less difficulty, you can treat people early on in the course of their disease so that their HIV reservoir is very small, and then you enhance the body’s own immune system, such as with therapeutic vaccination, to keep whatever virus remains in the body in check even after you discontinue antiretroviral therapy.

And so cure means being disease-free without noticeable virus replication in the absence of therapy. We are pursuing with our research agenda both eradication and functional cure. We have made a considerable investment all along in research pertaining to the kinetics of the HIV reservoir. And we have now committed $14 million a year over five years to [cure-focused research at] the new Martin Delaney Collaboratory because we really want to try to galvanize and catalyze the field.

**TA Report: Not long ago cure was kind of a dirty word—a fantasy—in AIDS research. Was there a moment in time when you suddenly thought, maybe this is possible after all?**
Dr. Fauci: It was not an “Aha!” moment where all of a sudden something happened. It was just my own experience as a physician, where I and many others were seeing so many patients who have been followed for years and whose virus is extraordinarily well contained. The studies of the reservoir showed that the earlier you treat, the smaller the reservoir. Patients were doing so well on antiretroviral drugs, and so the next logical question was, could we ultimately take them off drugs without relapses that we consistently saw when we tried to discontinue drugs in the past. It was just a gradually growing confidence in the capability of drugs to suppress this virus in a way that allows people to live a really, really long time. Also—looking from a broad 30,000-foot policy standpoint—with much greater numbers of people living with HIV today than ever before, it would be wonderful, given the constraints on resources, if we could get some of these people off therapy. Perhaps we could accomplish this with a different class of drugs or with a different approach.

**TA Report:** How do you see advances in cure-focused research reaching people in resource-limited settings?

Dr. Fauci: That is going to be a challenge, and it depends on the type of cure that we develop. We have a moral commitment to treat as many people as we can. But it is not incompatible to attempt to develop a cure at the same time as you are trying to treat as many people as you can in the developing world. I do not think that cure research is diverting away from the implementation of treatment programs. You do not want to pit basic research to try and find a cure against efforts to try and get as many people on treatment as possible. We are pursuing both approaches.

**TA Report:** There is a lot of debate right now about PrEP and its implementation. When many people in developing countries still don’t have access to antiretroviral drugs for treatment, how do you reconcile using ARVs for prevention with PrEP?

Dr. Fauci: That is a reasonable question, which is why I hold the opinion that PrEP is not for everyone. It is not one size fits all. There are certain groups of individuals whom you might want to target with PrEP. PrEP is not for every country or every situation within a country. It should be used selectively in targeted populations where you can get the most benefit.

**TA Report:** What is your biggest concern about the possible impact of budget cuts for HIV research at NIH?

Dr. Fauci: We have been fortunate, even though there have been great budgetary constraints, that we have not been hit hard by actual cuts. I am hopeful that this will continue. I believe there will be budget constraints for the next few years, and I will continue to try to make the case as forcibly as I possibly can that, in the arena of HIV, money invested in research now will ultimately save us a considerable amount of money in the future.

And the history of AIDS science has proven me correct over the years. An enormous amount of money is already being saved as a result of the transforming advances that we have made not only in treatment but also in prevention modalities we spoke about in the beginning of the interview. I think that makes a very strong case for investment in HIV science. Not only is it important in saving lives and preventing infection, but it is also going to save a lot of money in the future.

**TA Report:** And speaking of the future, a final question—given everything you know about research and the epidemic, how are we going to bring this global HIV epidemic to an end?

Dr. Fauci: I do not have a crystal ball, but I think we have some roadmaps. Number one: We have extraordinarily effective therapy. Number two: We now have scientifically proven, highly effective modalities for prevention. Number three: We now know that treatment itself can serve as a major form of prevention.

I think that if we get global, political, local, government, and private sector commitment, we can actually turn around and end this AIDS epidemic. I think we can do it, but we need that commitment, which is going to save not only a lot of lives but also a lot of money. The pandemic is not going to go away by itself.
to cervical and anal cancer—in HIV-positive adolescents. “We are already seeing a significant percentage of adolescents with HPV infection and abnormal Pap smear results,” said Dr. Jintanat Ananworanich, lead researcher on the project. “This highlights the need to embrace the reality that HIV-positive adolescents are having sex, and we must find ways to help them have safe sex.”

In addition to comparing HPV incidence between HIV-positive youth and their uninfected peers, Dr. Jintanat’s team is assessing risk for HPV infection among adolescents who contracted HIV through sexual behavior and those who were born with the virus and therefore have experienced a longer duration of immune suppression. Dr. Jintanat explained, “We know that in adults with HIV infection, immune suppression is a risk for cervical/anal cancer development.”

This study is expected to serve as the basis for future research that may ultimately impact the monitoring of cervical and anal cancer in adolescents in the region. Merck & Co., Inc. has made a generous donation of free HPV vaccine to HIV-NAT for this project. HPV vaccine is currently prohibitively expensive in most parts of Southeast Asia, and Dr. Jintanat hopes her team’s research will be a driving force to improve vaccine availability in the region.

Bone density loss
Sririraj Hospital at Mahidol University in Bangkok is collaborating with HIV-NAT to look at bone mineral density (BMD) levels in HIV-positive adolescents. “Low BMD causes fragility of the bone which leads to fracture risk, osteoporosis, and osteopenia,” explained Dr. Kulkanya Chokephaibulkit, lead researcher on the project at Sririraj Hospital. Bone mass accumulation occurs during childhood and adolescence, and normal BMD levels vary across geographic settings.

“Low bone mass density is associated with advanced HIV disease and use of protease inhibitors.”

Understanding how adolescents experience living with HIV
In order to aid clinicians in obtaining more honest and accurate personal information from HIV-positive adolescents, TREAT Asia is supporting a pilot study of an audio-computer-assisted survey instrument (ACASI) in Thailand and Malaysia. Researchers created a questionnaire about behavioral risk factors, stigma, and adherence to antiretroviral therapy based on models developed by the U.S. National Institutes of Health, U.S. Centers for Disease Control and Prevention, and the Thailand Ministry of Public Health. The questionnaire—offered in Malay, Chinese, and Thai—is administered privately and presented as a computer survey, with a digital recording that reads the questions aloud to the adolescent. The ACASI is expected to increase responsiveness by fostering a more comfortable environment in which adolescents with HIV may disclose personal details about adherence to medication, sex, drug use, and stigma.

These research investments are improving the understanding of long-term consequences of HIV infection and treatment for adolescents in Asia.