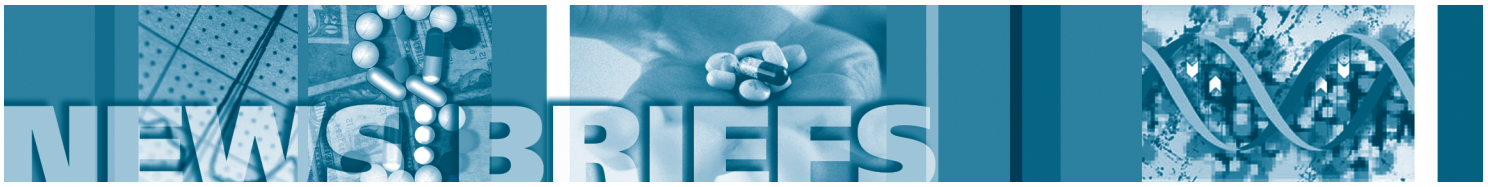

Liz Highleyman

CONFERENCE COVERAGE

The XVIII International AIDS Conference (AIDS 2010), a large biannual meeting encompassing all aspects of the HIV pandemic, took place July 18–23 in Vienna, Austria. The conference focused on the burgeoning epidemic in Eastern Europe and Russia driven largely by injection drug use.

With the theme "Rights Here, Right Now," the conference emphasized human rights issues related to criminalization of HIV transmission and the continued need for wealthy countries and private donors to support universal access to prevention and antiretroviral treatment in the face of the ongoing global financial crisis. Acknowledging that life-long antiretroviral therapy (ART) for millions of people worldwide is unlikely to be sustainable, participants also turned their attention to prospects for a cure.

The 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the National Minority AIDS Council's U.S. Conference on AIDS (USCA) took place in mid-September. ICAAC, held in Boston, focused on medical aspects of HIV and other infectious diseases, while USCA emphasized community-based responses to the epidemic.

Selected reports from these conferences are included below, along with recent news from medical journals and other sources.

ON THE WEB

AIDS 2010
www.aids2010.org

ICAAC 2010
www.icaac.org

2010 UCSA
www.nmac.org/index/usca-wrap-up

TENOFOVIR/EMTRICITABINE PREP SHOWS PROTECTIVE EFFECT

In late November, investigators released eagerly awaited data from the iPrEx trial showing that pre-exposure prophylaxis (PrEP) using tenofovir plus emtricitabine (the drugs in the Truvada combination pill) can help prevent HIV infection. A protective effect has previously been demonstrated in animal studies, but these are the first results from a human PrEP efficacy trial.

As described in the November 23, 2010, advance online issue of the *New England Journal of Medicine,* this Phase III trial enrolled nearly 2,500 men who have sex with men and a small number of transgender women in Brazil, Ecuador, Peru, South Africa, Thailand, and the U.S. (Boston and San Francisco).

Participants were randomly assigned to take oral tenofovir/emtricitabine or placebo once daily; in addition, they received monthly HIV testing, regular risk-reduction counseling, and free condoms.

During a median follow-up period of 1.2 years (maximum 2.8 years), 36 men using tenofovir/emtricitabine became infected compared with 64 men taking placebo—a risk reduction of 44%. Among participants who achieved at least 90% adherence, the likelihood of HIV infection fell by 73%.

"The iPrEx results are extremely important and provide strong evidence that PrEP can reduce HIV acquisition among a segment of society disproportionately affected by HIV/AIDS," said National Institute of Allergy and Infectious Diseases (NIAID) director Anthony Fauci during a media conference call to announce the findings.

"This study provides the first proof that oral PrEP works in people, and the first proof of any biomedical intervention to prevent infection in gay and bisexual men," added study chair Robert Grant from the University of California at San Francisco's Gladstone Institute of Virology and Immunology.

Tenofovir/emtricitabine was generally well-tolerated, although some participants reported moderate and usually short-lived nausea. Few people overall showed signs of impaired kidney function—a known potential side effect of tenofovir—but elevated serum creatinine occurred more often in the PrEP group compared with placebo (2% vs. 1%).

No emergent drug-resistance mutations were detected in participants newly infected during the study. Three PrEP recipients who were actually HIV infected but not yet antibody positive at study entry developed emtricitabine resistance.

Study participants did not increase their high-risk behavior because they thought they might be protected, but rather reported more condom use and fewer sex partners. Adherence proved difficult, however; drug-level tests suggested that about half the participants did not take their pills regularly. Only three people who became infected while on PrEP had measurable drug levels.

Researchers and community advocates emphasized that PrEP is not completely protective and should not be considered a replacement for condoms or other risk-reduction measures. Furthermore, a protective effect has only been demonstrated in one population, and it is not known whether these results will extend to women or injection drug users, for example.

"PrEP could be part of a comprehensive HIV prevention package in communities like ours with epidemics still disproportionately affecting gay men," said Judith Auerbach, San Francisco AIDS Foundation's Vice President of Research and Evaluation. (See "The iPrEx Results: Lifting Hopes, Raising Questions," page 47, for further commentary.)

Grant also noted that the iPrEx trial looked at PrEP used every day, not just before or after sex (as tested in the CAPRISA microbicide trial described below). "Whether oral PrEP can be used in this fashion is completely unknown at this time," he said.

Fauci advised that gay and bisexual men who wish to start taking tenofovir/emtricitabine off-label as PrEP should be aware of potential drawbacks. "[T]here is a clear possibility of long-range toxicities of the drugs," he cautioned. Fauci said he could not give a timeframe for when the U.S. Food and Drug Administration (FDA) might approve an additional PrEP indication for tenofovir/emtricitabine, or if or when antiretroviral treatment guidelines might be changed to recommend prophylactic use. Studies of PrEP in other populations, and of episodic rather than daily use, are underway.

TENOFOVIR MICROBICIDE REDUCES WOMEN'S HIV RISK

Perhaps the most welcome news at AIDS 2010 was a report by Salim Abdool Karim and fellow investigators with the CAPRISA 004 trial showing that a vaginal tenofovir gel offered women moderate protection against HIV infection during sex.

Prior microbicide studies in humans have not produced impressive results, but unlike earlier products, this gel is not just a physical barrier but contains an antiretroviral drug that actively inhibits HIV replication (marketed as Viread in its oral formulation).

As described at the conference and in the July 19, 2010, issue of *Science,* this Phase IIb trial included nearly 900 initially HIV negative women enrolled at two sites (one urban and one rural) in KwaZulu-Natal, South Africa. The women were sexually active, not pregnant, had no other sexually transmitted diseases, and were considered to be at high risk for HIV infection. They were randomly assigned to apply either 1% tenofovir gel or an inactive placebo gel, inserted into the vagina using pre-filled applicators, within 12 hours before and 12 hours after having sex.

Women using tenofovir gel had an HIV incidence rate of 5.6 new infections per 100 person-years, compared with 9.1 for participants using placebo gel. Overall, women using the microbicide had a 39% lower risk of becoming infected. Risk reduction reached 54% among participants who achieved good adherence, but fell to 38% for those with intermediate adherence and 28% for those with only poor adherence. Tenofovir gel also halved the risk of herpes simplex virus type 2 infection (the cause of genital herpes).

Tenofovir gel was generally well-tolerated without notable toxicities, including no increase in serum creatinine, a marker of impaired kidney function. Almost all study participants found the gel to be acceptable and said they would use it if it were shown to prevent HIV infection.

Based on these findings, the CAPRISA researchers concluded, "Tenofovir gel could potentially fill an important HIV prevention gap, especially for women unable to successfully negotiate mutual monogamy or condom use."

The study findings were widely heralded as the first demonstration that a microbicide can reduce HIV infection in humans under real-world conditions. But tenofovir gel is still in early development and is not expected to be available for at least a few years. With its safety and acceptability established, it will now move into larger Phase III efficacy trials.

The Microbicide Trials Network is currently conducting a related trial called VOICE, testing tenofovir gel applied daily rather than only at the time of sex. Advocates have also called for testing it as a rectal microbicide for anal sex. In early November, CONRAD, the agency spearheading the development of tenofovir gel, announced that the FDA has granted "fast track" status to enable faster review of studies.

"For the first time, we have seen results for a woman-initiated and -controlled HIV prevention option," said UNAIDS executive director Michel Sidibe. "If confirmed, a microbicide will be a powerful option for the prevention revolution and help us break the trajectory of the AIDS epidemic."

TESAMORELIN APPROVED FOR LIPODYSTROPHY

In November, the FDA approved tesamorelin (Egrifta; formerly known as TH9507) for treatment of a type of lipodystrophy in HIV positive people taking antiretroviral therapy. Tesamorelin is a synthetic growth hormone–releasing factor that stimulates the pituitary gland to secrete more human growth hormone.

Approval was based on clinical trials showing that daily tesamorelin injections significantly decreased visceral abdominal fat and lowered total cholesterol levels. The drug was generally well-tolerated and caused fewer side effects than growth hormone itself. For more information, see "Drug Watch: Tesamorelin Update," page 16.

ONCE-DAILY LOPINAVIR/RITONAVIR APPROVED

The FDA announced in late April the approval of once-daily 800/200 mg lopinavir/ritonavir (Kaletra) tablets and oral solution for use by previously treated HIV positive adults without extensive lopinavir resistance. Once-daily administration is not recommended for children or for adults with three or more lopinavir resistance-associated mutations.

Twice-daily lopinavir/ritonavir was initially approved for treatment-experienced patients in September 2000; once-daily dosing was later added for treatment-naive individuals. The new regimen is supported by data from Study 802, a Phase III randomized clinical trial showing similar efficacy and tolerability with once-daily and twice-daily dosing.

DEVELOPMENT OF THREE ANTIRETROVIRAL DRUGS HALTED

Given the effectiveness of current combination ART, it has become increasingly difficult for new drugs to demonstrate superiority to existing therapies in clinical trials.

In July, Merck announced that it was discontinuing development of its investigational CCR5 antagonist vicriviroc for treatment of HIV infection. Last January, the company announced that it would not seek approval of vicriviroc for treatment-experienced individuals. At the 2010 Conference on Retroviruses and Opportunistic Infections (CROI) last February, researchers reported that in the VICTOR trials, vicriviroc did not demonstrate noninferiority to an optimized background regimen plus placebo for this population.

This summer, the company announced that it has also decided to stop testing the drug for treatment-naive HIV patients, again due to unimpressive Phase II study results. All ongoing clinical trials of vicriviroc were terminated and participants were transitioned to other drugs. The company did not indicate whether it plans to pursue research on vicriviroc for other potential indications.

In related news, the Australian biotechnology company Avexa announced in May that it has stopped development of its investigational nucleoside reverse transcriptase inhibitor (NRTI) apricitabine after failing to find a licensing partner. While apricitabine demonstrated potent antiviral activity and good tolerability in a Phase IIb trial, its twice-daily dosing schedule puts it at a disadvantage compared with once-daily NRTIs such as abacavir (Ziagen) and tenofovir.

Finally, in June, Utah-based Myrexis (formerly Myriad Pharmaceuticals) said it is ending development of the HIV maturation inhibitor bevirimat, once known as PA-457 and renamed MPC-4326 when Myriad purchased it from Panacos in 2009. Bevirimat demonstrated promising activity in early studies, but the tablet formulation had poor bioavailability and response rates were lower than expected. Researchers later determined that HIV with specific genetic polymorphisms (variations) was more likely to respond, but about one-third of treatment-naive HIV patients showed decreased susceptibility to the drug. Myrexis indicated that it will suspend work on this class of HIV drugs and focus instead on cancer therapies.

EXPERIMENTAL ANTIRETROVIRAL DRUGS

RILPIVIRINE SHOWS POTENT ACTIVITY

Rilpivirine (TMC278), an investigational next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed by Tibotec, continued to show potent antiviral activity and good tolerability in previously untreated patients at 48 weeks, according to a pair of Phase III clinical trials presented at a late-breaker session at AIDS 2010 (*abstract THLBB206*).

Cal Cohen from the Community Research Initiative of New England reported pooled data from the ECHO (TMC278-C209) and THRIVE (TMC278-C215) trials. Together, these two multinational studies enrolled 1,368 treatment-naive participants. About 75% were men, 60% were white, and the median age was 36 years. The median CD4 cell count was about 250 cells/mm^3 and patients had no known NNRTI resistance-associated mutations.

In ECHO, 690 people were randomly assigned to receive 25 mg once-daily rilpivirine or 600 mg once-daily efavirenz (Sustiva) in combination with tenofovir/emtricitabine. In THRIVE, 678 participants were randomly assigned to the same doses of rilpivirine or efavirenz, but had a choice of NRTI backbones; 60% used tenofovir/emtricitabine; 30% used zidovudine/lamivudine (Combivir), and 10% used abacavir/lamivudine (Epzicom).

People taking rilpivirine and efavirenz were equally likely to achieve viral load suppression (below 50 copies/mL)—84% vs. 82%, respectively—among the highest rates observed in recent trials of first-line HIV treatment. CD4 cell gains were also similar (192 vs. 176 cells/mm^3).

Overall, 9% of rilpivirine recipients and 5% of efavirenz recipients experienced virological failure, with a larger difference in ECHO (11% vs. 4%). At ICAAC in September, researchers reported that treatment failure was linked to high baseline viral load and poor adherence (*abstract H-1810*).

But rilpivirine was associated with fewer side effects than efavirenz, especially central nervous system symptoms. About half as many rilpivirine recipients (16% vs. 31%) experienced moderate-to-severe adverse events considered possibly related to study drugs; 3% vs. 8%, respectively, discontinued therapy due to adverse events. Rilpivirine also had a more favorable lipid profile than efavirenz. Serum creatinine levels changed little in either group and there was no difference in QT interval changes, a type of heart rhythm abnormality.

About 60% of rilpivirine recipients and about 50% of efavirenz recipients developed new NNRTI-resistance mutations, but people taking rilpivirine were twice as likely to develop NRTI-resistance mutations.

Based on these findings, Tibotec announced that it has submitted a New Drug Application for rilpivirine to the FDA. Tibotec and Gilead Sciences are also jointly developing a single-tablet regimen containing rilpivirine plus tenofovir/emtricitabine, which was submitted for European regulatory approval in September.

TBR-652 INHIBITS HIV, MAY REDUCE INFLAMMATION

TBR-652, being developed by Tobira Pharmaceuticals, is a new CCR5 antagonist entry inhibitor that also blocks CCR2, another surface receptor on certain white blood cells. CCR2, which binds to monocyte chemoattractant protein 1 (MCP-1), appears to play a role in inflammation and has been linked to inflammatory conditions such as atherosclerosis.

At last February's CROI, Cal Cohen gave the first presentation on the drug, reporting that it had potent antiviral activity and it appeared to be safe and well-tolerated in a Phase II proof-of-concept trial (*abstract 53*).

The study included 54 HIV positive participants, mostly men, with exclusively CCR5-tropic virus and an average CD4 cell count of about 450 cells/mm^3. They were treatment-experienced but had been off ART for at least six weeks and had never used another CCR5 antagonist. Patients were randomly assigned to receive TBR-652 at doses of 25 mg, 50 mg, 75 mg, 100 mg, or 150 mg per day, or else placebo, for ten days.

By the end of the treatment period, TBR-652 at doses of 50 mg and higher suppressed HIV by at least 1 log (up to 1.8 log in the 75 mg dose group). The drug was well-tolerated with no severe adverse events, serious laboratory abnormalities, or deaths. The most common adverse events were gastrointestinal and flu-like symptoms.

At AIDS 2010, David Martin from Tobira reported further data from the same study, with an emphasis on TBR-652's inflammation-modulating effects (*abstract MOAB0104)*. MCP-1 levels increased in all TBR-652 dose groups (up to 300 pg/mL in the 150 mg arm)—which the researchers used as an indicator of effective CCR2 receptor blocking—but remained stable in the placebo group.

C-reactive protein (an inflammation biomarker) decreased on average, but this was mainly attributable to a single participant with a high baseline level. Interleukin 6 (IL-6) was undetectable in all participants, suggesting that the test may not have been sensitive enough.

Some audience members expressed concern that TBR-652 might interfere with immune response in ways that could increase risk of infections, as seen in prior animal and human studies of CCR2 blocking. Martin said no such increase in infections had been observed in TBR-625 trials so far. Tobira announced that it plans to start a Phase IIb clinical trial in early 2011 that will evaluate the effects of TBR-652 on immunological, cardiovascular, and metabolic parameters.

GSK572 INTEGRASE INHIBITOR SHINES IN PHASE II

S/GSK1349572—or GSK572 for short—is a second-generation integrase inhibitor being developed jointly by Shionogi and ViiV Healthcare. Prior research has shown that it works against HIV with some raltegravir-resistance mutations and has a high genetic barrier to resistance. According to data from two Phase IIb trials presented at AIDS 2010, the drug continues to demonstrate potent antiviral activity and good tolerability.

The SPRING-1 study (*abstract THLBB205*) included 205 previously untreated HIV patients. Most were men, 80% were white, and the median baseline CD4 cell count was 324 cells/mm^3. Participants were randomly assigned to receive GSK572 at doses of 10 mg, 25 mg, or 50 mg, or else 600 mg efavirenz once-daily. About two-thirds took tenofovir/

emtricitabine and one-third took abacavir/lamivudine as an NRTI backbone.

In a planned 16-week interim analysis, GSK572 demonstrated "rapid and robust" antiviral activity, with at least 90% of participants in all three dose arms reaching undetectable HIV RNA (below 50 copies/mL), compared with 60% in the efavirenz arm. Patients using GSK572 also took significantly less time to achieve viral suppression. CD4 cell gains ranged from 153 to 176 cells/mm^3 in the GSK572 arms, compared with 116 cells/mm^3 in the efavirenz arm.

GSK572 was generally well-tolerated; only 4%–8% of participants in the GSK572 arms experienced at least moderate drug-related adverse events, compared with 18% in the efavirenz arm.

VIKING was a smaller single-arm trial evaluating the safety and efficacy of GSK572 in 27 treatment-experienced patients, again mostly men, with pre-existing resistance to raltegravir (Isentress) and to any three antiretroviral drug classes (*abstract MOAB0105*). Participants in this study had more advanced HIV disease—with a median CD4 cell count of 110 cells/mm^3 and about 60% with a diagnosis of AIDS—and they had been on ART for a median of 14 years and taken a median of 17 drugs.

All participants first received 50 mg once-daily GSK572 as "functional monotherapy" (i.e., the only active drug) for 10 days, then background regimens were optimized and treatment continued through week 24. Overall, 78% of study participants achieved viral load below 400 copies/mL by day 11, with a mean HIV RNA drop of 1.45 log. But response differed according to pre-existing resistance. Just 33% of people with a Q148 mutation plus at least one secondary mutation achieved virological response, compared with all patients with N155 and Y143 mutations. Again, GSK572 was generally well-tolerated with no serious drug-related adverse events.

In October, Shionogi-ViiV announced the start of the GSK57 Phase III development program, including the SPRING-2 trial enrolling treatment-naive participants and the SAILING study enrolling treatment-experienced patients.

RALTEGRAVIR SAFE DURING PREGNANCY

Pregnant women with HIV can safely use raltegravir with no need for dose adjustment to account for changes in body size or blood volume, according to a study reported at ICAAC (*abstract H-1668a*).

Researchers looked at raltegravir pharmacokinetics in ten HIV positive women in the IMPAACT P1026s study, collecting data from the third trimester of pregnancy through six weeks after delivery. All women took the standard adult dose of 400 mg twice daily.

Raltegravir pharmacokinetic parameters varied widely among study participants, but none were significantly different for the pregnant women as a group compared with non-pregnant adults in prior studies; average raltegravir concentrations usually reached the target therapeutic level. The drug readily crossed the placenta and was detected in umbilical cord blood.

"Raltegravir exposure was not consistently altered during third trimester compared to post-partum and historical data, and the standard dose appears appropriate during pregnancy," the researchers concluded.

HIV TREATMENT GUIDELINES

ADULTS AND ADOLESCENTS

U.S. and global experts continue to issue updated guidelines for HIV treatment to reflect the latest study findings.

Coinciding with AIDS 2010, the International AIDS Society-USA (IAS-USA) released new antiretroviral treatment guidelines for adults, updating the previous version from 2008. Published in the July 21, 2010, *Journal of the American Medical Association,* these recommendations concur with those of the U.S. Department of Health and Human Services (DHHS), which advise that asymptomatic HIV positive people should initiate ART when their CD4 T-cell count falls to 500 cells/mm^3, with no upper limit.

Like the DHHS, the IAS-USA panel recommended starting with two NRTIs, preferably the fixed-dose tenofovir/emtricitabine pill (Truvada), along with either a ritonavir-boosted protease inhibitor, the NNRTI efavirenz (Sustiva), or the integrase inhibitor raltegravir (Isentress).

Once started, ART should not be interrupted except in the context of a clinical trial. People who experience virological failure should, if possible, switch to a regimen that includes at least two, and ideally three, fully active drugs in order to avoid resistance. Boosted protease inhibitor monotherapy should be avoided, the panel said.

The IAS-USA panel also recommended treatment for some groups regardless of CD4 cell count, including pregnant women, people older than 60 years, and people with coexisting conditions such as hepatitis B or C, HIV-associated kidney disease, or elevated cardiovascular risk. But the panel emphasized the importance of assessing individual readiness before starting therapy.

The panel weighed in on the ongoing debate about when to start treatment, noting that early ART may help control systemic inflammation and reduce the risk of HIV transmission (see next news item). "The prominence of non-AIDS events as a major cause of morbidity and mortality in those with ongoing HIV replication suggests

that early ART initiation may further improve the quality and length of life for persons living with HIV," the panel members wrote. The full IAS-USA recommendations are available online at ***http://jama.ama-assn.org/cgi/content/full/304/3/321.***

PREGNANT WOMEN AND BABIES

In May, DHHS released updated guidelines for treatment of pregnant women with HIV, intended both to benefit the woman's health and to prevent transmission of HIV to the baby. The new version did not include major changes, but added a new rating system and further information about drug resistance, safe delivery methods, and treatment of HIV positive pregnant women coinfected with hepatitis B. The revised guidelines are available at ***http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.***

The following month, DHHS issued updated ART guidelines for children with HIV, including a stronger recommendation that all infected babies under 12 months of age should start treatment, regardless of CD4 cell count or percentage. These guidelines are available at ***http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf.***

Revised World Health Organization (WHO) recommendations, issued last June, advise that exposed infants be tested for HIV by four to six weeks of age. All infected children under the age of two years should start antiretroviral treatment when diagnosed, again regardless of CD4 cell count or percentage or presence of clinical symptoms.

Between the ages of two and five years, HIV-infected children should initiate ART when their CD4 count falls to 750 cells/mm^3 or their CD4 percentage to 25% or lower. Children age five years and older should follow the latest WHO adult recommendation to start treatment when the CD4 count falls to 350 cells/mm^3.

This past fall, WHO released updated ART guidelines for pregnant women and infants who have received single-dose nevirapine (Viramune). This regimen is widely used in resource-limited settings to prevent mother-to-child HIV transmission—especially for women who do not receive care prior to delivery—but mothers and infants exposed to a single dose may develop drug resistance that can compromise future NNRTI therapy.

WHO therefore now recommends that women exposed to single-dose nevirapine within the past year should be treated with a combination ART regimen containing drugs other than NNRTIs, and babies should receive lopinavir/ritonavir (Kaletra).

This revision is supported by two studies published in the October 14, 2010, *New England Journal of Medicine.* The OCTANE A5208 trial analyzed 745 women in seven African countries who required ART for their own health.

Among women previously exposed to single-dose nevirapine, those subsequently treated with nevirapine-based combination ART were significantly more likely to experience virological failure or death than those using a lopinavir/ritonavir-based regimen. Looking only at women with identified nevirapine resistance mutations, the failure rates were 73% vs. 6%, respectively.

Nevirapine resistance and the associated risk of treatment failure diminishes over time, however, and the guidelines state that women can safely use nevirapine in a combination regimen one year after receiving a single preventive dose.

The second study, known as P1060, assessed treatment outcomes among 164 babies (up to three years of age) who were exposed to single-dose nevirapine during delivery or immediately after birth. Again, children subsequently treated with a nevirapine-based combination regimen were significantly more likely to experience virological failure or to discontinue treatment than those receiving lopinavir/ritonavir. Among babies with identified resistance mutations, the failure/discontinuation rates were 83% vs. 18%, respectively.

Study investigators concluded that alternative strategies for prevention of mother-to-child HIV transmission "are urgently required." The authors of an accompanying editorial, however, noted that single-dose nevirapine would continue to be used due to its low cost and widespread availability.

SAN FRANCISCO ADOPTS EARLY TREATMENT

This spring, San Francisco became the first U.S. city to adopt a policy of offering antiretroviral treatment to everyone who tests HIV positive, regardless of CD4 cell count. The policy was developed by clinicians with the Positive Health Program at San Francisco General Hospital (SFGH) and also applies to other facilities run by the San Francisco Department of Public Health (SFDPH). But the ultimate decision about starting ART remains with individual patients and their physicians, said outgoing SFDPH director Mitch Katz, who emphasized, "we don't dictate medical practice by policy."

The policy change is supported by a growing body of evidence indicating that early antiretroviral treatment can help prevent a variety of non-AIDS complications—including cardiovascular disease, neurocognitive impairment, and the appearance of faster aging—that occur before CD4 cell counts fall into the danger zone for opportunistic infections. (See "When to Start Treatment: A Changing Equation," *BETA,* Summer 2008, and "Inflammation, Immune Activation, and HIV," *BETA,* Winter/Spring 2010.)

"We should perhaps think of AIDS as acquired inflammatory disease syndrome," said SFGH researcher Steven Deeks. "The old paradigm was that drugs are toxic so we should wait as long as possible. The new paradigm is that while today's drugs are not totally benign, they are less toxic than the virus."

DHHS treatment guidelines adopted in December 2009 recommend starting ART within the 350–500 cells/mm^3 range, with 55% of the expert panel considering this a strong recommendation and 45% considering it moderate; above 500 cells/mm^3, the panel was evenly divided, with half favoring treatment initiation and half deeming it optional.

While Katz and the SFGH doctors emphasized that the motivation behind the new policy is benefits for individual patients, another possible advantage of early treatment is reduced HIV incidence. ART can lower viral load to an undetectable level, which dramatically decreases the risk of passing on the virus.

Mathematical models have suggested that universal testing and early treatment could potentially halt the epidemic. Real-life studies have begun to provide evidence that expanded testing and treatment lowers "community viral load" and the number of new infections. At AIDS 2010 and in the August 14, 2010, issue of *The Lancet,* for example, Julio Montaner's team at the British Columbia Centre for Excellence in HIV/AIDS reported that increased treatment of injection drug users was associated with a recent drop in HIV incidence in British Columbia.

But this raises concerns about a potential conflict between individual and public health benefits. "Test-and-treat" skeptics fear that people could face mandatory testing and be pressured to start treatment—with its attendant cost, inconvenience, unknown long-term toxicities, and risk of drug resistance—before they need it for their own health.

"It is unethical and irresponsible to coerce or encourage people who are not recommended for treatment under the guidelines to start therapy without fully informing them of the risks," wrote *POZ* magazine founder Sean Strub.

The San Francisco-based HIV/AIDS advocacy group Project Inform has endorsed a "testing and linkage to care plus" (TLC+) strategy, encouraging people to learn their status and enter care to address all their health and psychosocial needs, only then considering the benefits and drawbacks of ART.

The New York-based Treatment Action Group, in contrast, has declined to take a position on early ART, preferring to wait for data from controlled studies such as the START trial (see "Open Clinical Trials," page 51). In this trial, HIV positive people with a CD4 count above 500 cells/mm^3 will be randomly assigned to either initiate ART immediately or when their CD4 count falls to that level.

As reported at AIDS 2010 (*abstract THLBB201*), an analysis of more than 9,000 HIV positive people in the multinational CASCADE cohort found that participants who started ART with a CD4 count in the 350–500 cells/mm^3 range had a significantly lower likelihood of progression to AIDS or death than people who deferred treatment. But starting treatment above 500 cells/mm^3 did not reduce the risk any further.

While START looks for individual benefits of early therapy, NIAID has launched pilot programs in the Bronx and Washington, D.C., to see if a test-and-treat approach can reduce HIV rates on a community-wide basis.

On a global scale, UNAIDS included "treatment as prevention" as part of its Treatment 2.0 strategy, announced this summer in Vienna. This approach could potentially prevent up to one million new HIV infections per year if ART is made available to all who need it based on the latest WHO guidelines, tripling coverage from the current 5 million to 15 million people, the agency estimated.

SEARCH FOR A CURE

A cure for HIV appears more scientifically feasible than ever, and its urgency remains undiminished despite highly effective antiretroviral treatment, according to presentations at AIDS 2010 and at a preceding meeting sponsored by the International AIDS Society, titled "Toward a Cure: HIV Reservoirs and Strategies to Control Them."

While ART has dramatically reduced illness and increased survival, people with HIV still do not achieve a normal life expectancy, Sharon Lewin from Monash University in Melbourne said at the AIDS 2010 opening plenary.

A growing body of evidence indicates that chronic immune activation and inflammation due to persistent HIV infection can lead to a host of problems throughout the body despite suppressed viral load and well-preserved immune function. In addition, even modern antiretroviral medications still have long-term toxicities. Finally, funding universal life-long treatment for millions of people worldwide appears increasingly unsustainable.

Ultrasensitive tests show that almost all HIV positive people with "undetectable" HIV RNA have a small amount of residual virus. Researchers continue to debate whether this is mainly attributable to low-level ongoing viral replication or release of latent virus from resting CD4 T-cells. But to date, neither starting ART during very early infection nor ART intensification—adding extra drugs to an already suppressive regimen—has succeeded in eliminating HIV.

In the November 27, 2010, issue of *AIDS,* for example, Tae-Wook Chun and Anthony Fauci from NIAID and colleagues reported that even people who started antiretrovi-

ral drugs during acute HIV infection and maintained viral load suppression for a decade still had detectable viral genetic material in resting CD4 cells using the most sensitive tests. One man with a very small reservoir of CD4 cells harboring latent HIV—estimated at 1 per 1.7 billion—still experienced viral rebound 50 days after interrupting ART.

A growing number of researchers from government, academia, and the pharmaceutical industry are looking at a variety of approaches to either completely eradicate HIV from the body or achieve a functional cure by disabling the virus or strengthening the immune system.

Investigators have looked at a variety of agents that can activate resting cells and force gene expression and release of latent virus, making it susceptible to antiretroviral drugs. Several studies have shown that histone deacetylase (HDAC) inhibitors such as valproic acid and vorinostat can flush latent HIV out of hiding, and work is underway to develop related drugs that can safely be used by HIV positive people who remain healthy on ART.

Another strategy involves altering CD4 cells to make them resistant to HIV. This approach was inspired in part by the "Berlin Patient," an HIV positive man who received a bone marrow stem cell transplant to treat leukemia. Gero Hütter, a German hematologist, located a donor with the naturally occurring CCR5-delta32 mutation, which protects cells from HIV entry. Three years after the first transplant, the man shows no evidence of remaining virus in his blood, resting cells, or reservoir sites such as the gut.

While widespread bone marrow transplantation is not realistic, researchers have tried to build on this proof-of-concept in other ways, such as altering cells using gene therapy to make them HIV-resistant. One method now being studied in clinical trials involves removing CD4 T-cells from a patient, using zinc finger technology to remove a gene for the CCR5 coreceptor, and returning the altered cells to the body.

Altering the hematopoietic stem cells that give rise to CD4 cells and other immune cells would likely be a longer-lasting—possibly lifelong—approach. In the August 2010 issue of *Nature Biotechnology,* Paula Cannon from the Keck School of Medicine at the University of Southern California and colleagues reported that humanized mice given genetically engineered CCR5-deleted stem cells and then exposed to HIV showed little CD4 cell loss or disease progression.

In a related human study described in the June 16, 2010, edition of *Science Translational Medicine,* John Zaia and colleagues at City of Hope Medical Center tested a similar technique in four HIV positive people undergoing stem cell transplants to treat lymphoma.

Patients' stem cells were removed and altered in three different ways to make them resistant to HIV. After cancer chemotherapy destroyed the remaining immune cells in the body, the altered stem cells were reintroduced. The modified cells were successfully engrafted and no adverse side effects were seen. This particular approach, however, remains too risky for people who do not require such drastic therapy for a life-threatening condition.

This past June the National Institutes of Health announced the creation of a new public/private collaboration, named after Project Inform founder Martin Delaney, that will support research on HIV persistence and eradication. An initiative to fund cure research was also recently launched by amfAR.

NATURAL HIV CONTROLLERS

People who naturally control HIV long-term without antiretroviral drugs—estimated at about one in 300 people infected with the virus—have a distinct pattern of amino acid variations in genes encoding HLA proteins, which enable the immune system to recognize and respond to invading pathogens and virus-infected cells.

As reported in the November 4, 2010, advance online edition of *Science,* investigators with the International HIV Controllers Study performed a genome-wide association analysis that included nearly 1,000 HIV controllers and 2,600 people with normal progressive HIV disease. The researchers identified several specific amino acid substitutions in the HLA-B peptide binding groove that were associated with protection against disease progression.

These results, the researchers suggested, imply that the interaction between HLA and viral peptides is a key to durable control of HIV. "We found that, of the three billion nucleotides in the human genome, just a handful make the difference between those who can stay healthy in spite of HIV infection and those who, without treatment, will develop AIDS," said Bruce Walker from the Ragon Institute of Massachusetts General Hospital, MIT, and Harvard. "Understanding where this difference occurs allows us to sharpen the focus of our efforts to ultimately harness the immune system to defend against HIV."

"HIV is slowly revealing its secrets, and this is yet another," he continued. "Knowing how an effective immune response against HIV is generated is an important step toward replicating that response with a vaccine. We have a long way to go before translating this into a treatment for infected patients and a vaccine to prevent infection, but we are an important step closer."

BONE LOSS COMMON, SCREENING ADVISED

Several recent studies looked at low bone mineral density among people with HIV. At AIDS 2010 (*abstract THPDB104*),

ICAAC 2010 (*abstract H-226*), and in the November 27, 2010, issue of *AIDS,* Anna Bonjoch from University Hospital German Trias in Barcelona and colleagues reported that about half of a Spanish cohort of 671 HIV positive people on ART had osteopenia (mild-to-moderate bone loss), while about one-quarter had the more severe osteoporosis.

Among 391 participants who had at least two DEXA scans, 28% experienced progressive bone loss during a median follow-up period of 2.5 years (13% from normal to osteopenia, 16% from osteopenia to osteoporosis). Significant predictors of bone loss included older age, male sex, low body mass index, and longer use of tenofovir or protease inhibitors.

In related research presented at AIDS 2010, Richard Haubrich and fellow ACTG Study 5142 investigators (*abstract WEAB0304*) compared changes in bone density among people taking various ART combinations. Participants taking all regimens experienced bone mineral loss, but some were worse than others.

People who took tenofovir experienced significantly more bone loss than those taking zidovudine (AZT, Retrovir) or stavudine (d4T, Zerit), while those taking a lopinavir/ritonavir protease inhibitor–based regimen had a trend toward more bone loss than those using an efavirenz NNRTI-based regimen.

In the September 10 issue of *AIDS,* Marlous Grijsen from the University of Amsterdam and colleagues reported that men with primary, or very early, HIV infection already had low bone density in the spine and hip compared with an HIV negative reference population. In a study of 33 newly infected men (average age 38 years), 45% had osteopenia and 6% had osteoporosis; though the study was small, the risk appeared to increase with higher viral load.

Turning to the clinical significance of reduced bone density among people with HIV, two recent studies produced conflicting results. At the 1st International Workshop on HIV and Aging in Baltimore in October, researchers from GlaxoSmithKline (*abstract O_07*) presented an analysis of more than 200,000 participants enrolled in the Ingenix Impact National Benchmark Database; 59,584 HIV positive people, about half of them on ART, were each matched with three HIV negative individuals.

During follow-up, 4.2% of HIV positive participants sustained new non-traumatic fractures (bone breaks not caused by trauma such as accidents) compared with 3.7% of HIV negative participants, for an incidence rate ratio of 1.14, or 14% higher risk.

Factors significantly associated with fracture risk included prior fractures, low physical activity, low body weight, heavy alcohol consumption, and use of bisphosphonates (a class of drugs used to manage bone loss). Among middle-aged people (30–59 years), HIV infection was an additional risk factor. The likelihood of fractures increased significantly more with advancing age among HIV positive people with or without AIDS compared with HIV negative participants.

But another recent study, published in the November 13, 2010, issue of *AIDS,* did not see an increase in fractures among 1,728 mostly premenopausal HIV positive and 663 at-risk HIV negative participants in the Women's Interagency HIV Study (WIHS).

Over a median follow-up period of about five years, 8.6% of HIV positive women and 7.1% of HIV negative women sustained new fractures; incidence rates were 1.8 and 1.4 per 100 person-years, a difference that did not reach statistical significance.

Significant fracture risk factors included older age, white race, hepatitis C coinfection, cigarette smoking, and opiate use. However, there was no observed link between fractures and use of any antiretroviral drug class or particular drugs, including tenofovir.

In the October 15, 2010, issue of *Clinical Infectious Diseases,* Grace McComsey and an international team of experts recommended that all HIV positive women who have reached menopause and all HIV positive men age 50 or older—as well as those with a history of past fragility fractures—should undergo DEXA bone density screening every two to five years. Those with prior fragility fractures (but not traumatic fractures) should be screened regardless of age. In contrast, recent guidelines from the National Osteoporosis Foundation recommend bone screening for women over 65 and men over 70 with no risk factors.

Individuals with signs of bone loss should consider treatment such as alendroate (Fosamax) to improve bone density and prevent further loss, the authors advised. To reduce the risk of bone problems, the authors recommended that HIV positive people quit smoking, take calcium and vitamin D supplements, get adequate sun exposure, and exercise regularly. However, they concluded that there is "currently no evidence" to suggest that switching to different antiretroviral drugs can improve bone density or lower fracture risk.

CANCER AND HIV/AIDS

Evidence continues to accumulate showing that people with HIV and AIDS may develop cancer earlier and more often despite antiretroviral treatment, but study results are not entirely consistent. (For an overview, see "A Glass Half Full: Cancer Risk for People Living with HIV," page 30.)

As reported at AIDS 2010 (*abstract WEAB0101*), Meredith Sheils, Eric Engels, and colleagues from the National

Cancer Institute (NCI) extended their previous research on changing rates of AIDS-defining and non-AIDS-defining cancers in the ART era.

The investigators looked at rates of cancer among people with HIV and AIDS, with incidence (new cases) determined by linking CDC HIV/AIDS data and cancer registries in 15 areas of the U.S. Rates for people with AIDS were estimated using data from 1991–2005, while those for people with HIV but not AIDS were estimated using data from states with confidential name-based HIV reporting since 2004.

Thanks to widespread adoption of ART in the mid-1990s, the total number of people living with AIDS increased from 93,802 (8% of them age 50 or older) in 1991 to 399,762 (29% age 50 or older) in 2005. During 1991–2005, a total of 76,558 cancer cases were reported in this population.

Cases of AIDS-defining cancer—primarily Kaposi's sarcoma and non-Hodgkin lymphoma—declined steeply, from 7,284 in 1993 to 1,736 in 2005. In contrast, non-AIDS cancers increased over time as people with AIDS lived longer, from 416 cases in 1991 to 2,437 in 2005. Anal and prostate cancer rates rose, while incidence of lung cancer and Hodgkin's lymphoma remained relatively stable.

During 2004–2007 in the 34 states with consistent name-based reporting, there were 4,388 cases of cancer among people with HIV (but not necessarily AIDS), including 892 cases of lung cancer, 381 cases of anal cancer, and 327 cases of Hodgkin's lymphoma.

"Dramatic increases in non-AIDS-defining cancers among persons with AIDS are driven by growth and aging of the AIDS population, and rising incidence rates for some cancers," the researchers concluded, adding that, "Cancer prevention and treatment in HIV-infected persons are increasingly important."

In a related study published in the August 9, 2010, *Archives of Internal Medicine,* NCI researchers assessed long-term cancer risk among people with AIDS relative to the general population. Analyzing medical records from more than 263,000 adults and adolescents with AIDS during 1980–2004, they saw an increased risk for all non-AIDS-defining cancers considered together, as well as for several specific malignancies, including Hodgkin's lymphoma, mouth and throat cancers, anal and penile cancer, and lung cancer.

An Italian study published in the November 1, 2010, issue of *Clinical Infectious Diseases* reached a similar conclusion. Antonella Zucchetto and colleagues compared rates of non-AIDS malignancies among 10,392 HIV positive people diagnosed with AIDS during 1999–2006 and members of the general population matched for age and sex.

Over a median follow-up period of 37 months, 7.4% of all deaths among people with AIDS were due to non-AIDS cancers—more than six times higher than the general population rate. The most common malignancies leading to death in people with AIDS were lung cancer, liver cancer, Hodgkin's lymphoma, and head and neck cancers.

Compared with the general population, people with AIDS had elevated mortality rates for several non-AIDS cancers, including anal cancer (270 times higher likelihood of death), Hodgkin's lymphoma (174 times higher), liver cancer (11 times higher), and brain and central nervous system cancers (10 times higher).

People with AIDS had especially elevated risk of death due to cancers with an infectious cause, including anal cancer (caused by human papillomavirus or HPV), Hodgkin's lymphoma (linked to Epstein-Barr virus), and liver cancer (often caused by chronic hepatitis B or C viruses).

Turning to another aspect of cancer risk, the NCI team compared ages at the time of diagnosis of non-AIDS cancers among people with AIDS and the general population. As reported in the October 5, 2010, *Annals of Internal Medicine,* an analysis of data from more than 212,000 people with AIDS during 1996–2007 showed that the age at diagnosis of most types of cancer was not significantly different for people with and without AIDS after adjusting for age and other factors.

But people with AIDS were significantly younger than the general population, on average, when diagnosed with lung cancer (median 50 vs. 54 years) and anal cancer (42 vs. 45 years), and significantly older when diagnosed with Hodgkin's lymphoma (42 vs. 40 years).

Minh Ly Nguyen from Emory University School of Medicine and colleagues (*AIDS 2010 abstract WEAB0105*) also looked at age at the time of cancer diagnosis, retrospectively analyzing data from 8,300 people with HIV (but not necessarily AIDS) seen at an urban HIV clinic in Atlanta between 2000 and 2007; only about half were on combination ART.

A total of 512 patients were diagnosed with cancer during this period, a majority (320 cases) being AIDS-defining cancers, especially Kaposi's sarcoma. Incidence rates for most non-AIDS cancers were significantly higher for people with HIV compared with the general population, though this was not the case for prostate or breast cancer. Except for Hodgkin's lymphoma, these cancers were diagnosed 10–15 years earlier, on average, in HIV positive people compared with the general population.

Among the 192 cases of non-AIDS malignancies, 40% were lung cancer (diagnosed at an average age of 52 years in HIV positive people vs. 66 years in the general population), 24% were anal-rectal cancer (age 41 vs. 55), 22%

were head and neck cancers (age 51 vs. 61), 18% were prostate cancer (age 53 vs. 64), 16% were Hodgkin's lymphoma (age 40 vs. 42), 11% were breast cancer (age 45 vs. 58), and 10% were liver cancer (age 44 vs. 60).

The researchers concluded, "Many non-AIDS-defining cancers occur at an increased rate compared to the general population and at an earlier age." Again, this was particularly true for malignancies caused by viruses. They therefore recommended that cancer screening for people with HIV "should be considered at an earlier age."

RAPID LIVER DISEASE PROGRESSION

People who are already HIV positive when they become infected with hepatitis C virus (HCV) may experience unusually rapid liver disease progression, according to a poster presented at the American Association for the Study of Liver Diseases (AASLD) annual Liver Meeting, held in Boston October 29–November 2, 2010.

For the past decade, clinicians in the U.K. and Europe, and later the U.S. and Australia, have reported clusters of apparently sexually transmitted acute HCV infection among HIV positive gay and bisexual men. It is known that people with HIV/HCV coinfection tend to experience more rapid liver disease progression than those with hepatitis C alone, especially if they have a low CD4 cell count; however, a subset of coinfected individuals may experience very aggressive liver disease.

Daniel Fierer and colleagues from Mt. Sinai Medical Center in New York City presented follow-up findings on four members of a small cohort of HIV positive men with acute HCV infection and advanced liver disease, first described at the 2007 CROI.

Initially diagnosed during the acute stage of HCV infection (identified due to elevated liver enzyme levels), these four HIV positive men, all with HCV genotype 1a, went on to develop chronic infection. One patient received pegylated interferon plus ribavirin but experienced treatment failure, another could not tolerate therapy, and two refused treatment. The men's ages ranged from 39 to 54 years, and their CD4 counts were highly variable, at 53, 200, 381, and 442 cells/mm^3.

Even though they had very early hepatitis C, three of the men already had advanced (stage F3) fibrosis on their first liver biopsy and progressed to liver cirrhosis (stage F4) by the second biopsy; the fourth man had stage F2 fibrosis on the first biopsy and did not receive a second test. The men did not show evidence of tissue damage suggesting liver toxicity due to antiretroviral drugs.

All four men progressed to decompensated cirrhosis (liver failure) within 14 to 78 months after initial liver enzyme elevation—a process that typically takes many years or even decades in HIV negative hepatitis C patients. Of note, two did so despite relatively high CD4 cell counts. At the time of the report, one man had received a liver transplant, another was still alive after six years but had persistent cirrhosis symptoms, and two had died of liver failure.

These cases indicate that "early onset fibrosis after HCV infection of HIV-infected men is not benign, does not spontaneously resolve, and can quickly progress to cirrhosis, liver failure, and death," the researchers concluded. "It is therefore essential to identify, treat, and cure all HIV-infected men with new HCV infection to prevent these dire outcomes."

ONE-FIFTH OF U.S. GAY MEN HAVE HIV

Nearly 20% of gay and bisexual men in 21 large U.S. cities are HIV positive, but more than 40% do not know their status, according to study findings described in the September 24, 2010, *Morbidity and Mortality Weekly Report*.

Investigators from the CDC collected data from the National HIV Behavioral Surveillance system on HIV prevalence among men who have sex with men (MSM), defined as having had sex with another man at least once during the past year. The analysis included more than 8,000 men in 21 metropolitan statistical areas surveyed during 2008. Participants completed anonymous interviews and received HIV blood tests.

Overall HIV prevalence (total infections) was 19%. Rates were highly variable across cities, however, ranging from 6% in Atlanta to 38% in Baltimore. Early epicenters of the epidemic had above-average to high rates, including Chicago (19%), Los Angeles (19%), San Francisco (23%), and New York City (29%). Several higher-prevalence cities were located in the south, including Dallas (26%), Houston (26%), Miami (25%), and New Orleans (21%). But Washington, D.C.—often cited as one of the most heavily impacted cities—was below average at 14%.

Looking at demographic factors, men who identified as homosexual and bisexual had similar HIV prevalence rates (19% and 18%, respectively), more than twice as high as self-identified heterosexuals (8%). Prevalence rose with increasing age—from 7% among men age 18–19 up to 28% for the 40–49 age group and 25% for those age 50 or older.

Consistent with other studies, African Americans had the highest prevalence (28%), Asians had the lowest (8%), and whites and Hispanics were in between (16% and 18%, respectively). Prevalence fell as education level and income increased.

Overall, 44% of the men who tested HIV positive as part of this study had not previously known they were in-

fected. By self-identification, 39% of homosexual men knew their status compared with 63% of men who said they were bisexual or heterosexual. Racial/ethnic disparities were again apparent, with 59% of black men, 46% of Hispanics, 43% of Asians, and 26% of white men not knowing they were positive. Lack of awareness was especially high among young men, reaching 75% for the 18–19 age group.

"Because MSM represent the only group with increasing HIV incidence and comprise the largest proportion of new infections, it is critical to target resources and prevention strategies to MSM," the study authors wrote.

LATE ACCESS TO HIV CARE

Not knowing one's HIV status can have serious health consequences, according to another recent study published in the June 1, 2010, issue of *Clinical Infectious Diseases.* Keri Althoff from Johns Hopkins University and colleagues analyzed data from 44,491 HIV positive participants in the NA-ACCORD study, collected between January 1997 and December 2007.

The median age when first accessing HIV care increased over time, from 40 years in 1997 to 43 years in 2007. The median CD4 count also rose during this time span, from 256 to 317 cells/mm^3. The percentage of people with a CD4 cell count of at least 350 cells/mm^3 (the threshold for starting ART at the time of the analysis) increased from 38% in 1997 to 46% in 2007—but this still left 54% of participants eligible to start treatment when they first sought care. African Americans had a lower initial CD4 cell count than whites or Hispanics, on average, and they were more likely to be immediately eligible for ART.

WHITE HOUSE RELEASES NATIONAL HIV/AIDS STRATEGY

On July 13, 2010, President Barack Obama unveiled the first-ever National HIV/AIDS Strategy for the United States. Speaking at a White House press conference and reception for members of the HIV/AIDS community, the president said, "We have learned what we can do to stop the spread of the disease. We've learned what we can do to extend the lives of people living with it. So the question is not whether we know what to do, but whether we will do it."

The plan focuses on several areas, including resource allocation to the most heavily affected populations, science-based policy, and greater coordination of prevention, testing, and care. The document opens with an overarching goal: "The United States will become a place where new HIV infections are rare, and when they do occur, every person, regardless of age, gender, race/ethnicity, sexual orientation, gender identity, or socio-economic circumstance will have unfettered access to high-quality, life-extending care, free from stigma and discrimination."

The plan was informed by more than 4,000 people who participated in public discussions hosted by the White House Office of National AIDS Policy (ONAP) or submitted comments to the ONAP website. Input came from medical and social science experts, AIDS care and service providers, and HIV positive people and advocates from across the country.

"This represents the work of thousands of individuals whose leadership and input over the last three years helped it take shape," said San Francisco AIDS Foundation's Judith Auerbach, a cofounder of the Coalition for a National AIDS Strategy. "Now it is up to all of us to ensure its full funding and implementation and hold our government accountable for progress."

Advocates were generally pleased with the content of the strategy, but disappointed that it did not come with significant new funding—versus reallocation of existing money—for its implementation.

The National HIV/AIDS Strategy and accompanying materials are available online at ***www.aids.gov/federal-resources/policies/national-hiv-aids-strategy.***

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