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TAG
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tagline

NEWS ON THE FIGHT FOR BETTER TREATMENT, A VACCINE, AND A CURE FOR AIDS

World Health Organization HIV Treatment Guidelines Evolve

Safer and more effective drug combinations included in new guidelines

BY MARK HARRINGTON

Unusually, there was something to celebrate on World AIDS Day in 2009, even if it was only on paper. The World Health Organization (WHO) updated its antiretroviral treatment (ART) guidelines for adults, adolescents, pregnant women, mother-to-child transmission, and breast-feeding. These guidelines were issued in late November 2009.[1] The new WHO guidelines are progressive and reflect changes in knowledge and practice which have also been reflected over the past year in revised ART guidelines in Europe, South Africa, the United Kingdom, and the United States, among others. TAGline will cover the new WHO ART guidelines for adults and adolescents here; future articles will examine issues related to children, pregnancy, breastfeeding, and evolving ART guidelines in specific countries.

The new WHO ART guidelines are the first to be released since 2006. Among the key changes in the new guidelines are a higher CD4 cell level for initiating ART from ≤200 to ≤350 CD4 cells, including pregnant women and people with tuberculosis (TB). This move brings the WHO guidelines more in synch with the most recent ART recommendations in developed nations.

The panel addressed several other key issues with this update:

- Replacing stavudine (d4T) in first-line therapy with tenofovir or AZT, something advocates have long called for. The writing group *"…placed high value on avoiding the disfiguring, unpleasant and potentially life threatening toxicity of d4T"*
- Starting ART as soon as possible after initiating TB treatment for HIV-positive people with active tuberculosis (TB) disease, which kills 500,000 people with HIV each year.

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NIAID Workshop: Elimination of HIV Reservoirs

BY RICHARDS JEFFERYS

On Friday, January 15, the National Institutes of Allergy & Infectious Diseases (NIAID) sponsored a scientific workshop entitled "The Next Challenge: Elimination of HIV Reservoirs." The event took place during the Keystone conference on HIV pathogenesis in Santa Fe, New Mexico. The focus of the agenda was on curing HIV infection, a goal once thought far-fetched but recently made to seem more attainable by a case of apparent HIV eradication, described at the workshop by Jeffrey Laurence in a talk entitled: "Proving the Concept: The First Well-Documented Functional, and Probably Complete, Case of HIV Eradication."

The individual in this case—which received considerable media attention last year—is an American living in Berlin

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- Starting ART regardless of CD4 count for people coinfected with hepatitis B (HBV) and HIV, using regimens containing both tenofovir and lamivudine (3TC) or emtricitabine (FTC) to reduce the risk of HBV resistant mutations. However, the lack of viral hepatitis screening in many parts of world remains a major barrier. The management of both HBV and hepatitis C virus (HCV) must be integrated into the global standards of care for HIV, as hundreds of millions of people worldwide are infected with these killer hepatitis viruses.

- Using HIV RNA (viral load) testing to guide the decision to switch to second-line ART. This change will support the scale-up of viral load testing in developing countries. HIV RNA monitoring is critical for diagnosing HIV infection among newborns and to avert the 50% mortality seen within two years when they are untreated. HIV RNA measurement is useful to detect non-adherence or virologic treatment failure. In developed countries, repeated detectable viral load increases demonstrate treatment failure and lead to a therapy switch. Hitherto most developing countries (though Brazil and South Africa are exceptions) have not widely used viral load testing because of its cost. However recent data demonstrate that when people are switched to second-line ART on the basis of CD4 cell loss or clinical progression, virologic failure is often advanced and the virus may have developed additional resistance mutations. Yet, the main reason for reluctance to switch in many countries may be the expense or lack of access to second-line therapy, which usually includes a boosted protease inhibitor (such as atazanavir or lopinavir with ritonavir) plus two nucleoside analogue reverse transcriptase inhibitors (NRTIs). In the absence of viral load technology, the WHO strongly recommends initiating HIV therapy regardless, and switches based on CD4 cell loss or clinical progression.

- National programs should consider introducing third-line therapies when first- and second-line regimens fail. While this could be expensive, introducing third-line regimens would bring the global standard of care much closer to that prevailing in developed countries. The WHO panel suggested including more recently approved treatments in third-line therapy such as an integrase inhibitor or newer non-nucleoside RTIs (NNRTIs) or protease inhibitors. Unfortunately, many of these agents are not yet approved or affordable in most developing countries.

The new WHO guidelines do not change the recommended first-line ART anchor NNRTI agent—either efavirenz or nevirapine—with a background of tenofovir (TDF) or zidovudine (AZT) with 3TC or FTC. This presents new complications when starting treatment at higher CD4 counts. Nevirapine is not safe to initiate in women with over 250 CD4 cells (or in men with over 400) due to a higher risk of liver toxicity, while efavirenz is contraindicated in the first trimester of pregnancy due to concerns of neural tube defects in the fetus. Since many women do not know they are pregnant during their first trimester, this complicates the selection of the safest treatment choice when starting ART at a CD4 count of over 250. Data from the antiretroviral pregnancy registry do not suggest that there is an excess of such defects in babies born to mothers taking efavirenz. However, new options that lack either danger would be welcome in this situation.

These new guidelines are more progressive than those of the previous version, and will vastly increase the estimated number of people who need treatment. This in turn makes the achievement of universal access to HIV treatment—defined as treating at least 80% of those who need ART—by the end of 2010 even more unlikely. Meeting the universal access target under the 2006 guidelines would have required putting 6 million more people on treatment by the end of 2010. With the new higher CD4≤350 as the ART starting recommendation, one would need to perhaps quadruple the number currently on therapy from 4 to 16 million.

In the next five years, over 10 million people will die of AIDS unless treatment scale-up —enrollment of new ART participants— continues and those on current programs stay enrolled. There is an AIDS funding backlash which claims that treating people with ART is too expensive. It is necessary to point out, however, that for every increase in the proportion of HIV-positive people put on therapy, there is in fact a certain (but not yet precisely measured) decrease in the likelihood of onward transmission of HIV. If applied widely enough, this approach (treating HIV earlier) has the potential, when combined with other effective prevention methods, to reverse the spread of HIV and even perhaps to bring the epidemic under control, though it is unlikely that in the absence of a vaccine that the HIV pandemic can ever be fully eliminated.

The WHO's new HIV treatment guidelines offer plenty of promise in a time of uncertainty about the future of the fight against HIV. Recommendations call for better, safer, and more effective drug combinations to be made available earlier and much more widely for all people with HIV; scale-up of better monitoring technology including viral load is recommended; and the potential for quantifying the effect of expanding HIV treatment to limit HIV transmission thus changing the dynamics of the pandemic is emerging. A tipping point for the pandemic appears to be coming into focus. It would be tragic if world leaders decide now is the time to stop scaling up the fight against HIV. ●

1. World Health Organization. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents – November 2009. www.who.int/entity/hiv/pub/arv/rapid_advice_art.pdf.

Other References:

World Health Organization. Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants, November 2009. http://www.who.int/entity/hiv/pub/mtct/rapid_advice_mtct.pdf.

World Health Organization. Rapid advice: revised WHO principles and recommendations on infant feeding in the context of HIV – November 2009. http://whqlibdoc.who.int/publications/2009/9789241598873_eng.pdf.

For updates see the WHO HIV ART guidelines site: http://www.who.int/hiv/pub/arv/advice/en/index.html.

Two new classes of TB drugs—the first in 40 years—advance through phase II studies

Progress brings hope for TB treatment but many challenges emerge

BY CLAIRE WINGFIELD

After 40 years of scientific stagnation, it is beginning to be an exciting time in tuberculosis treatment research.

Tuberculosis (TB) is the leading killer of people with HIV worldwide, accounting for more than quarter of all HIV deaths in 2008 according to the World Health Organization (WHO). That same year, more than 5%—that is, 500,000—of all recorded TB cases were confirmed as multidrug-resistant (MDR), meaning those individuals were infected with a form of the disease that has developed resistance to the two most common and powerful first-line TB drugs, isoniazid and rifampicin. Most cases of MDR-TB are never diagnosed because many laboratories—particularly those where lots of people with TB and HIV live with limited resources—lack the proper diagnostic tools, trained staff, and infrastructure to detect drug resistance. Reported cases of MDR-TB are just the tip of the iceberg, and a scant 3% of people with MDR-TB receive proper treatment, in accordance with WHO guidelines.

While first-line treatment for drug-susceptible TB has a cure rate of 95% in well- functioning TB programs, treatment for MDR-TB cures only 50–70% of cases, and requires 18–24 months of complicated, expensive, and often toxic combination therapy. Depending on the drug sensitivity profile of the TB bacteria, as well as country-specific drug availability, a person may be required to take up to six different pills multiple times per day, as well as a painful injection. This complex treatment regimen can cause a long list of side effects, not the least of which includes psychosis. The need for better, shorter, more effective, and more tolerable treatment for drug-susceptible and drug-resistant TB is urgent and acute.

Since the heyday of TB drug development in the 1950s and '60s, no new class of TB drugs has been approved to treat the disease. However, over the past few years TB drug development has experienced a minor renaissance. Seven drug candidates with novel mechanisms of action against TB are in human studies, most to treat MDR-TB, and two broad-spectrum antibiotics are under widescale evaluation for drug-susceptible TB. Two of the drugs farthest along in the TB pipeline are Tibotec Pharmaceuticals' TMC207

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and Otsuka Pharmaceuticals' OPC-67683. Both drug candidates are in phase II clinical studies for treatment of drug-resistant TB. The Global Alliance for TB Drug Development (aka the TB Alliance) is planning to initiate phase II studies of its nitroimidazole, PA824, within the year. The other three new compounds in phase I human trials are Sequella's SQ-109, which is a diamine, Pfizer's PNU-100480, and AstraZeneca's AZ5847, which are both oxazolidinones, along with the already approved (for sepsis) linezolid (Pfizer's Zyvox), which is being looked at in low doses for MDR-TB.

TMC207, a diarylquinoline, and OPC-67683, a nitroimidazole, are from wholly new treatment classes (as are the oxazolidinones); thus it is possible that these two drugs could potentially be combined to enhance treatment of drug-resistant TB. Since four out of these seven drugs are from new and different classes there is potential for synergy among them against both drug-susceptible and drug-resistant TB.

Tibotec released promising, preliminary data from the first stage of a phase II study showing that adding TMC207 to a standard MDR-TB treatment regimen reduced the amount of TB bacteria faster than the standard regimen alone after eight weeks of treatment. A second stage is evaluating TMC207 plus a standard background regimen versus placebo plus a background regimen for 24 weeks. Any volunteers diagnosed with extensively drug-resistant TB, before the six-month treatment period is over will be given open-label TMC207.

For the first time in history, Tibotec has begun an open-label safety study for a TB drug. The study currently has three sites up and running in South Africa, with other potential sites in Russia, Eastern Europe, and Asia. The trial will enroll up to 225 people with confirmed MDR-TB. Enrollment has been slow, and local regulatory requirements have proven to be a challenge to scale-up studies. In addition, the lack of data on drug-to-drug interaction between TMC207 and certain antiretroviral (ARV) drugs has delayed enrollment of people who are taking ARVs. The US Adult AIDS Clinical Trials Group (AACTG) is looking at the pharmacokinetic (PK) interactions of TMC207 with one of the most commonly used ARVs, efavirenz, and Tibotec is conducting PK studies of TMC207 with nevirapine and (separately) with lopinavir/ritonavir (Aluvia, Kaletra). Sponsors need to accelerate the PK studies that will make it clear which ARV drugs can be used safely with the new TB drugs, as the interaction between TB disease and advanced HIV can be fatal unless both diseases are effectively treated together.

Each country has its own regulatory agency and process, and therefore its own rules and requirements for approving and registering new treatments. Sponsors

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of TB drug trials often cite the lack of clarity on local regulatory requirements (particularly in high-burden settings) as a major impediment to the rapidity of initiating clinical trials. Because there has not been a TB drug registration trial since the 1960s, there is little to no experience in conductingand monitoring these type of studies in the TB field.

Because so few people can enter controlled clinical trials, TAG and other activists including the Treatment Action Campaign (South Africa) and the European AIDS Treatment Group (EATG) have called for TB drug developers to conduct, when enough safety data exist, open-label safety studies for those without other treatment options and who cannot enroll in controlled trials. This early form of expanded access was used in the early days of AIDS drug development and was known as compassionate use (while later, broader expanded access programs opened to a broader population when drug activity became clearer). Given the low success rate of treatment for drug-resistant TB, the high burden of disease, and the increased risk for death among people coinfected with HIV and TB, these new compounds that may shorten treatment and result in better treatment outcomes should be made available to those who are not eligible for trials but are in desperate need of effective treatment. The reluctance to make these newer compounds available through compassionate-use programs stems from the fear that releasing them will lead to unregulated use and development of drug resistance before the drugs even make it to market. This is compounded by a lack of access to drug susceptibility testing (DST) in many high-burden settings, making it difficult to determine the most effective regimen for each person.

These concerns are valid, yet there is a need to confront these challenges and strategize on how best to introduce new compounds while maximizing their benefit without jeopardizing future use. Expanded-access issues are new to TB programs and service providers as there have not been any new compounds to consider for treating TB in either its drug-susceptible or drug-resistant forms for many years.

Given the dearth of effective treatment options, the time has come to make these treatments more readily available—especially for those with hard-to-treat MDR-TB disease, in program settings with good patient care, DST, and appropriate background combination treatments. ●

As with HIV Treatment, Botswana Leads the Way with TB Prevention

BOTUSA study strongly supports continuous preventive IPT for people with HIV

BY JAVID SYED

Tuberculosis (TB) remains the leading cause of death among people living with HIV. The World Health Organization's 2009 report *Global Tuberculosis Control: Epidemiology, Strategy, Financing* reported that in 2007, 1.4 million new cases of TB occurred in people living with with HIV/AIDS (PLWHA), and that it accounted for nearly a quarter of all deaths among the HIV-positive population. The high levels of mortality and the high burden of TB disease among people with HIV clearly points to the urgent need to fully implement interventions that can prevent TB transmission and the progression from TB infection to TB disease in PLWHA.

Among the interventions most clearly proven to be effective in preventing the progression of TB infection to disease are antiretroviral therapy (ART), which strengthens immune control of latent TB infection, and preventive therapy with isoniazid (INH), which directly eliminates the TB bacillus from the body and, while taken, may prevent reinfection. A six- to nine-month course of INH, a first-line TB drug, is one intervention that has been shown to be effective in preventing TB disease in people with HIV. Yet despite the mountain of evidence that shows the efficacy of isoniazid preventive therapy (IPT) in reducing risk for progression to TB—especially in people with HIV—the implementation of IPT programs is shamefully low. In 2008, countries reported to the World Health Organization (WHO) that only 4.1% of their estimated HIV-positive patients were screened for TB, and IPT was provided to just 0.2%.

The challenge of being able to rule out the presence of active TB among immune-compromised people with HIV is a significant barrier to the roll-out of IPT, since treatment of active disease with any monotherapy promotes the emergence of drug resistance. Several other issues need to be addressed to clarify how best to implement IPT: determining how best to rule out active TB disease; when to initiate treatment; whether there are important additive drug toxicities with ART; and determining the optimal duration and post treatment protective effect of IPT. In the past five years, new data have emerged that address these challenges. The WHO created an algorithm for the diagnoses of smear-negative and extrapulmonary TB to provide a roadmap to treat the disease among those without smear- or culture-confirmed disease, which includes all children and most people with HIV. Data from Brazil, South Africa, and Thailand have shown that IPT has an additive benefit when given before and alongside ART. Despite valid questions about how to best implement IPT, the lack of political will has been a major impediment to its roll-out. Instead of demonstrating leadership by using best practices to ensure access to IPT, most HIV and TB programs in high–TB/HIV-burden

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settings have simply refused to implement this effective and lifesaving therapy.

Breaking the mold of stagnation and inaction that has limited IPT in most countries, Botswana has carried out both a national scale-up of IPT among its HIV-positive population and a controlled clinical trial comparing 6 months versus 36 months (intended to be a surrogate for lifelong therapy) of IPT among people with HIV. Just as Botswana broke the mold and started providing universal access to ART for its HIV infected people in the early 2000s, in the later part of the decade they moved to implement IPT and study its utility to limit the impact of TB among those with HIV. This study was called BOTUSA. The leadership from the government of Botswana is commendable. Data from the BOTUSA study, conducted in Botswana in partnership with the U.S. Centers for Disease Control and Prevention, were presented at the 40th World Lung Health Conference in December 2009.

The BOTUSA study was conducted from 2004 to 2009 to answer the primary question of whether IPT taken for 36 months was more effective than a 6-month course in reducing risk of TB disease in people with HIV. This study also provided critical information for addressing other IPT-implementation-related issues. The study involved a sample size of 2,000 people, who were randomized to receive either 6 or 36 months of 300 mg of INH daily with 25 mg of vitamin B6. Of these 2,000 people, 821 were assigned to six months of IPT, and 834 to 36 months in the intent-to-treat analysis of the study, which is more likely to reflect the outcomes that can be expected in routine program settings.

The results of the study as reported on December 7, 2009, included:

- Thirty-six months of IPT was more effective than 6 months and reduced the risk of TB disease by 56%.
- The protective effect of IPT waned 6–7 months after the end of treatment in both the 6-month and the 36-month arms.
- Adherence rates of IPT were high, at 78% at 31–36 months.
- The rate of INH resistance was lower in the 36-month arm, at 14%, compared with 17% in the 6-month arm, providing additional data to show that IPT does not lead to greater INH resistance.
- In people with HIV who had a negative tuberculin skin test (TST), the test commonly used to detect latent TB infection, 36 months of IPT alone reduced the risk of TB disease by 8%, but when given with ART, TB risk declined by 50%.
- IPT reduced the risk of TB disease much more dramatically in TST-positive people. Thirty-six months of IPT alone reduced the risk of TB disease by 92% and by 96% when used in combination with ART..

The study results have significant implications for the roll-out of IPT. Findings from the study support treatment with IPT for up to 36 months. IPT should be given continuously, before and during ART, for at least 36 months and probably lifelong, or at least until a patient's CD4 count reaches and stays at 500 CD4 cells or higher, the threshold at which TB rates are roughly the same as those for people not infected with HIV.

IPT is clearly more effective in people with HIV who have a positive TST; thus, a TST would be useful to target IPT to those most likely to benefit. However, the TST is not routine in many program settings; it does not identify TB infection among those with low CD4 counts, it requires refrigeration, it requires the patient to return to the clinic within 72 hours to have the results read, and it could become an additional barrier to scaling up IPT. Therefore, it should be used when available, but when it is not, IPT should be given to all HIV-infected persons without active TB disease.

On January 25–27, 2010, the WHO convened an expert meeting to prepare guidelines for IPT and for intensified case finding. TAG and its activist colleagues participated avidly in the heated discussion to ensure that the strong data supporting the critical need for IPT scale-up were recognized by the global panel, which included several conservative TB progammers who were reluctant to "add to the health worker workload" despite the fact that it is easier for both patient and provider to give a single drug to a healthy person than four drugs for six months to someone who is sick, not to mention that 500,000 people with HIV die each year—unnecessarily—of TB, a disease which is clearly both preventable and curable. Now the burden is on various countries' HIV and TB programs to expedite uptake of IPT, along with intensified case finding, infection control, and ART, for TB prevention among people with HIV.

As the BOTUSA study shows, IPT can make a critical contribution toward reducing the burden of TB disease among people with HIV. IPT is a low-cost, relatively simple intervention that can save tens of thousands of lives. The WHO is revising its guidelines for IPT to support its uptake and has also clarified that IPT should be the responsibility of national AIDS programs, which need to work with TB programs and communities of people living with HIV and TB to ensure that IPT is implemented successfully and with high rates of continuation. As Botswana has shown both with ART and with IPT, strong political will at the country level, accompanied by bold action, is urgently needed in order to take full advantage of the protection that IPT offers people with HIV so that they do not continue to die of curable TB. ●

1. WHO and Stop TB Partnership. 2009 Tuberculosis Update Facts. http://www.who.int/tb/publications/2009/tbfactsheet_2009update_one_page.pdf. Accessed February 7, 2010.

2. Golub JE, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. AIDS. 2009 Mar 13;23(5):631–6.

3. World Heath Organization, *Global Tuberculosis Control: A Short Update to the 2009 Report*. Available at http://www.who.int/tb/publications/global_report/2009/update/tbu_9.pdf. Accessed February 17, 2010.

NIAID, continued from page 1

who developed acute myeloid leukemia requiring a complex series of treatments over the course of more than a year, including chemotherapy and two stem cell transplants, along with an attendant regimen of immune-suppressive drugs to prevent transplant rejection and graft-versus-host disease (see box for a list).

Treatments Received
fludarabine, cytarabine, amsacrine, total body irradiation, antithymocyte globulin (ATG), cyclophosphamide, cyclosporine, mycophenolate mofetil, gemtuzumab

His treating clinician, Gero Hütter, identified 232 potential stem cell donors based on HLA matching and screened 80 of them in order to find an individual homozygous for the CCR5delta32 genotype, knowing that the cells from such a donor lack CCR5 expression and therefore might offer an additional benefit to his HIV-infected patient. A donor was found and, at the second attempt, the stem cells successfully engrafted leading to a complete remission of the acute myeloid leukemia and the repopulation of the individual's immune system with CCR5-negative cells. Antiretroviral therapy (ART) had to be stopped during the procedures and, after the engraftment, Hütter was surprised to observe that HIV viral load did not reappear and consequently ART did not need to be restarted.

The first report on the case appeared relatively quietly, as a poster at the Conference on Retroviruses & Opportunistic Infections in 2008 (abstract #719). One of the first people to pick up on it was Martin Delaney of Project Inform, who wrote an article for PI Perspective after the conference. A full case description was subsequently published by Hütter and colleagues in the New England of Medicine last February; at that time, the individual had been followed for 20 months off ART with no HIV DNA or RNA detectable in blood or tissues (N Engl J Med. 360;7:692-8, 2009).

At the NIAID workshop, Jeffrey Laurence was able to report that follow up is now out to 1,053 days – close to three years. HIV remains undetectable in both blood and tissues and the CD4 count is around 800, the highest level since the individual was diagnosed with HIV infection in the 1990s (at the time of the acute myeloid leukemia diagnosis, his CD4 count was 415). After a difficult period of post-transplant recuperation complicated by encephalopathy, the individual is now reported to be regaining health and hopes to soon return to work.

Laurence emphasized his belief that this case represents a compelling proof-of-concept that a cure for HIV infection can be achieved, but also acknowledged the complex set of circumstances involved and the difficulty of delineating all the potential contributing factors. He noted that efforts are underway to assess whether the result can be duplicated; although acute myeloid leukemia is relatively rare, there are likely to be a number of cases every year in people with HIV. Laurence is hoping that there will be another case in which a donor homozygous for CCR5delta32 can be identified, but he stressed that limits on the number of potential stem cell donors that can be screened in the US make this difficult (insurance typically will pay for only 2-10 screens).

In terms of the underlying mechanism for the apparent cure, Laurence stated that leading explanation is simply that, in the absence of the CCR5 co-receptor, HIV had nowhere to go. The immune suppression required to facilitate transplantation might also have depleted HIV reservoirs. There was some evidence that the individual had a minor population of HIV that was CXCR4-tropic (entered cells via the CXCR4 co-receptor as opposed to CCR5) at baseline, and the question was raised as to why this virus did not take over; Laurence acknowledged that there is no proven explanation but noted that the X4 tropism was inferred from the genetic sequence of the virus which may not always accurately predict co-receptor usage. Laurence also cited data published by Lokesh Agrawal a few years ago, which showed that in some individuals homozygous for the CCR5delta32 genotype, infection with both primary X4 and R5 viruses is inhibited, seemingly due to the CCR5delta32 protein downregulating expression of the X4 co-receptor. Additional analyses are being conducted in an attempt to ascertain definitively whether CXCR4-using viruses were present in the individual at baseline.

Carl June from the University of Pennsylvania gave a talk on a less invasive approach to creating a population of CCR5-negative T cells in HIV-infected people. June is conducting a pilot study in which CD4 T cells are sampled from individuals and then manipulated in the laboratory with a technique that snips out the CCR5 gene (the technique was developed by Sangamo Biosciences and involves molecular scissors called zinc fingers). The CCR5-negative CD4 T cells are then re-infused back into the same individual in hopes that they will preferentially survive and expand, providing a population of HIV-resistant cells.

Laurence emphasized his belief that this case represents a compelling proof-of-concept that a cure for HIV can be achieved.

June was only able to report data from the first study participant, who has experienced an increase in overall CD4 T cell numbers and also an increase in the population of CCR5-negative CD4 T cells to numbers greater than those originally infused, indicating that the cells can persist and divide in vivo (the proportion of CCR5-deleted CD4 T cells detectable in the peripheral blood rose from around 1% initially to 2.1% at 140 days of follow up). However, even with this expansion, the CCR5-negative CD4 T cells make up only a minority of the overall CD4 T cell pool. June also noted that HIV viral load rebounded to detectable levels during a pre-planned exploratory interruption of ART. The study is ongoing and due to

be completed in 2012. In terms of the practicality of the approach, the total cost of the procedure involved was cited by June as $15,650.

The task of providing a big-picture overview of the challenges involved in curing HIV infection fell to Janet Siliciano, a researcher at Johns Hopkins who has pioneered the study of long-lived HIV reservoirs in the body. Siliciano outlined three deceptively straightforward-sounding tasks that need to be accomplished:

- Ensure HIV replication is fully suppressed
- Identify all HIV reservoirs (cells containing integrated HIV)
- Develop strategies for eliminating each HIV reservoir

Siliciano reviewed the data suggesting that in most people on combination ART, the first goal has been achieved. This question has been controversial because in most people whose viral load is undetectable using standard assays (which measure down to 50 copies/mL), some residual viral RNA can usually be detected using ultra-sensitive tests which can pick up even a single HIV genome. There has been debate as to whether this residual virus results from ongoing cycles of HIV replication that ART is failing to stop, or rather reflects production of virions by long-lived infected cells which ART cannot impact.

As also described at the workshop by Sarah Palmer (who developed the ultra-sensitive single viral copy assay), most studies that have explored the impact of intensifying treatment have reported no impact on residual viral load, suggesting that ART is typically fully suppressive. The only caveat was offered by Javier Martinez-Picado, who reported data from a small intensification study using the integrase inhibitor drug raltegravir. In this study, about a third of the 45 participants randomized to receive treatment intensification showed evidence of ongoing replication at baseline, which was curtailed by the addition of raltegravir to their regimen.

Addressing the second and third tasks, Siliciano cited data from her group indicating that while the majority of latently HIV-infected cells are long-lived memory CD4 T cells, there also appears to be a stable second source of virus in many individuals that has yet to be identified, but may be a stem cell or long-lived macrophage. The viruses produced by this second source can be identified on the basis that they are genetically identical over time but also genetically different from the virus found in memory CD4 T cells.

Siliciano listed some of the strategies that have been tried to date to deplete HIV reservoirs, without much success. These include approaches that cause mass activation of memory CD4 T cells, which were horribly toxic, and modifiers of gene expression called HDAC inhibitors that might have the potential to eject integrated HIV DNA from an infected cell's genome. The latter approach, in the form of the drug valproic acid, was initially reported to lower the numbers of latently HIV infected cells in a small trial, but subsequent larger studies have found no effect (other HDAC inhibitors are still under consideration).

The Holy Grail for cure research as Siliciano explained, is to find an agent or agents that can selectively target only those cells containing HIV.

The Holy Grail for cure research, as Siliciano explained, is to find an agent or agents that can selectively target only those cells containing HIV. As attention refocuses on the possibility of curing HIV infection, the search for this grail is intensifying. The next major workshop addressing the state of research into curing HIV infection is being chaired by Nobel prize winner Francoise Barre-Sinoussi immediately prior to the 2010 International Conference on AIDS in Vienna. TAG will report back from the workshop later this year and continue to track the research as it progresses. ●

Related Webcasts from CROI

A number of presentations at the recent Conference on Retroviruses and Opportunistic Infections addressed the issue of whether HIV replication persists on ART, with the findings echoing those presented at the NIAID Workshop. Webcasts of the sessions are available online at the link below. Among the Friday webcasts, look for the themed discussion "Impact of Treatment Intensification on HIV Reservoirs and Immune Activation" which took place at 1:00pm. Later the same day is a talk from Frank Malderelli from the National Cancer Institute's HIV Drug Resistance Program entitled: "HIV Cure: Is it Realistic?"

http://www.retroconference.org/2010/data/files/webcast_2010.htm

HIV Research Catalyst Forum
TREATMENT • PREVENTION • ADVOCACY

Sponsorships are still needed for the HIV Research Catalyst Forum: Treatment, Prevention, Advocacy, April 20-23, 2010 in Baltimore, Maryland

The Catalyst Forum aims to revitalize the community response to the domestic and global AIDS epidemic by amplifying the voices of community advocates in HIV treatment and prevention research. This four-day conference will provide a rare opportunity for new advocates to gain knowledge, build capacity, and sharpen skills; for experienced advocates to exchange ideas, craft strategies, and tackle new challenges; and for advocacy networks to recruit new participants and collaborators to strengthen planned or ongoing research advocacy campaigns.

Sponsorships are available at the $2,500 and $5,000 level. For information on sponsorship, go to *http://hivresearchcatalystforum.org/cosponsors* ●

TAG Goes to Cuba

Cuba boasts model health outcomes but at what costs to human rights?

BY COCO JERVIS

In November 2009 TAG's senior policy associate, Coco Jervis, attended the Global Forum for Health Research meeting in Havana, Cuba, under a special license that permits U.S. citizens to go to Cuba for professional meetings sponsored by international organizations. The forum brought together more than 900 researchers, clinicians, advocates, entrepreneurs, and government health ministers from over 85 countries to discuss global health research innovation to improve health equity for the poor and disadvantaged.

As a leader in TB/HIV research and development investment tracking, TAG was invited to a preconference satellite meeting organized by the Global Forum to discuss the challenges of tracking resources for health research. Speakers focused on the need for more research investment in health systems strengthening and neglected diseases, the current backlash against global HIV spending and other disease specific research investments, the need for better guidelines for cross-country comparisons of investments in health research, and how to leverage health research investment data more effectively in health research advocacy.

As the hosts of the Global Forum, Cuban government officials showed little humility showcasing their own remarkable achievements in the public heath sector despite limited resources. With the guarantee of free and universal heath care for everyone—which many conference goers duly noted as doctors pounced on anyone who dared to enter the country with a sniffle or flushed face—the entire Cuban health care system is tiered with a reliance on wellness, holistic care, prevention of disease realized via watchdog zeal, and, at times, draconian measures. Case in point: Cuba boasts the lowest HIV rate in the Western Hemisphere, with only 2,700 HIV-positive people in the entire country as of 2007, according to UNAIDS statistics. Cuba's shockingly low HIV rate (whatever the true prevalence) belies a haunting reality that Cuban officials still firmly argue to justify the widespread violations of human rights which took place during the forced quarantine programs that lasted until the early 1990s. (Other violations of human rights including institutionalized homophobia are also well documented). Nowadays, treatment for HIV-positive people is said to take place at the community level, with daily clinic visits required for all those newly diagnosed and mandated (under the threat of detention), and treatment adherence monitored via house calls made by doctors and nurses who live in the community. These same clinicians are the gatekeepers for upward referrals to more specialized care, and they convene quarterly with community leaders to discuss health issues within the community. Despite the fact that taxi drivers and hotel clerks make more money then do government-paid clinicians and health researchers (Cuba boasts that they are one of the few developing countries that can provide a comprehensive supply of generic HIV medicines to their people), medicine remains a highly respected profession.

Cuba's public health system and its health care delivery model underscores the reality that despite limited resources much can be accomplished in improving health outcomes via strong (indeed, often coercive) political will. But, the central question remains: At what costs, and who gets to decide? As the HIV/AIDS community can attest, Cuba's authoritarian approach to protecting public health tramples the human rights of people living with HIV. As conference attendees left Cuba to return home and continue wrestling with the myriad of problems that block better research and universal access to health for people around the globe, the Cuban contradiction that juxtaposes the good of the public against individual rights underscored the critical need for community advocacy everywhere to ensure that the path leading to universal access to health is not perverted in the name of achieving it. Human rights, public health, and social justice must be advanced together under a common framework that puts the individual and community rights to dignity, health, and full participation in society at the center of work for a more just society.

Do The Right Thing

Eliminating Racial Disparities in Viral Hepatitis Drug Development

BY LEI CHOU AND TRACY SWAN. PRESENTED AT HEP DART 2009

"Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research.... conceptions of justice are relevant to research involving human subjects."

—The Belmont Report, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979

As with HIV, African Americans bear a disproportionate burden of viral hepatitis. Hepatitis C virus (HCV) is twice as prevalent, and hepatitis B virus (HBV) is nearly five times more prevalent among African Americans than Caucasians. The death toll from viral hepatitis complications, such as liver cancer, is almost twice as high among African Americans versus Caucasians.

These grim statistics prompted TAG's Lei Chou and Tracy Swan to investigate racial disparities in viral hepatitis drug development. They found that African Americans comprised less than 4% of all participants in eight phase III viral hepatitis treatment trials.

Adequate enrollment of African Americans matters, for scientific, practical and ethical reasons. For instance, researchers have been trying to figure out why HCV treatment is less effective for African Americans than Caucasians. Recent research identified a genetic polymorphism associated with favorable response to HCV treatment that is more common in Caucasians than African Americans. This important discovery would not have been possible without an adequate number of African American study participants.

Chou and Swan also analyzed factors contributing to racial disparities, and offered ways to address them. In December 2009, they presented their findings as a poster, called *Do The Right Thing: Addressing Racial Disparities in Viral Hepatitis Drug Development* at the HEP DART meeting. HEP DART is focused on viral hepatitis drug development; it is attended by a mixture of researchers, clinicians, basic scientists, epidemiologists, activists and investors. ●

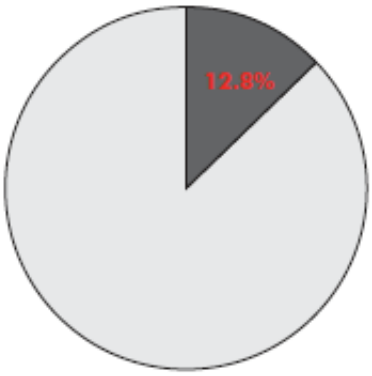
Resources:

Do The Right Thing is available on-line at: http://www.treatmentactiongroup.org/uploadedFiles/Projects/Hepatitis_C_-_HIV/HEPDART09%20letter.pdf

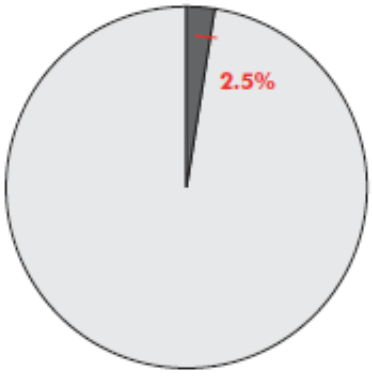
HEP DART information available on-line at: http://www.informedhorizons.com/hepdart2009/default.aspx

Underrepresentation of Underrepresented Minorities in Academic Medicine: The Need to Enhance the Pipeline and the Pipe. Merchant JL, Omary MB. Gastroenterology November 2009. Available on-line at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508509020344.pdf

According to published data from phase 3 trials involving U.S. participants, an average of 2.5% of enrollees in eleven HBV studies and 3.8% of enrollees in two HCV studies were African-American.



Estimated Population of African-Americans in the United-States, 2007
Source: 2007 Population Estimates, July 2007, U.S. Census Bureau.



Percentage of African-Americans Enrolled in Phase 3 HBV Clinical Trials

Percentage of African-Americans Enrolled in Phase 3 HCV Clinical Trials

President Obama's Disappointing 2011 Budget Presents Sharp Gap Between Needs and Funds Available

Negligible Increases for AIDS, TB, Viral Hepatitis Treatment and Research

BY SUE PEREZ

On Monday, February 1, 2010, President Barack Obama unveiled his fiscal year (FY) 2011 budget to the U.S. Congress. Global health programs were allocated $8.513 billion, a 9.4% increase over the FY2010 final funding level, yet the percent increase for global AIDS, domestic HIV prevention and domestic AIDS treatment programs received small increases of 3.5%, 4.25% and 1.7% respectively.

Domestic HIV prevention programs got a slight boost of $31 million and the critical Ryan White HIV/AIDS Treatment Program was allocated a mere additional $40 million. These minor increases signal disappointingly weak support for expanding prevention and treatment programs to control the domestic HIV epidemic.

Global tuberculosis (TB) programs received a paltry 2% increase of $5 million over the 2010 level. New monies for TB and HIV push the level of funding for TB and for TB-HIV coinfection to approximately $390 million, which is less than half of the $800 million authorized annually for global TB by Congress over the current five years of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).

The allocation for the Global Fund to Fight AIDS, Tuberculosis and Malaria, a vital funder of global AIDS, TB and malaria programs, was cut by $50 million. This is a distressing omen that the Obama administration is backing away from its commitment to support developing countries to reach universal access to prevention, treatment and care for the three diseases.

The Global Fund faces a multi-billion dollar gap and has been unable to fully fund all sound proposals submitted. The result will be counted in lives lost—existing HIV programs do not have enough money to enroll new patients who urgently require antiretroviral treatment and existing patients are experiencing treatment interruptions. Progress to increase the numbers of people tested for HIV is being threatened because people are hearing that treatment is not available, and the newly diagnosed or newly ill have no place to receive appropriate care.

Funding for domestic TB programs received a disappointing decrease of $1.2 million, and domestic viral hepatitis programs received an abysmal increase of $1.8 million (less than 1%) for FY2011. More than four million Americans live with chronic viral hepatitis, and there is no cure for hepatitis B.

President Obama requested an additional $1 billion for the National Institutes of Health (NIH) in FY2011 for a total of $32.089 billion—of which $3.2 billion will likely go toward AIDS research. This small increase (less than the actual amounts spent in 2009, when NIH received an approximately $5 billion increase from the stimulus package), while greater than funding levels proposed for many other federal agencies, fails to support needed funding increases to fulfill Obama's campaign promise to double the budget of the entire NIH. Without bold action by Congress, the disappointing reality is that the President's proposed 2011 budget for HIV, TB, and viral hepatitis research lacks the commitment and leadership required to stimulate new and innovative research over the long term. ●

Key Agency Numbers from President Obama's FY2011 Budget to Congress

Agency / Health Area	FY2009 Enacted	FY2010 Obama Request
National Institutes of Health	$31.089 billion	$32.089 billion (+$1B)
Global Fund to Fight AIDS, Tuberculosis and Malaria	$1.050 billion	$1 billion (-$50M)
Global AIDS (including PEPFAR)	$5.088 billion	$5.268 billion (+$180M)
Domestic AIDS Prevention	$728 million	$759 million (+$31M)
Domestic AIDS Treatment (Ryan White AIDS Program)	$2.290 billion	$2.330 billion (+$40M)
Global TB	$246 million	$251 million (+$5M)
Global TB/HIV*	~$140 million	~$140 million
Domestic TB	$144.2 million	$143 million (-$1.2M)
Domestic Viral Hepatitis	$19.3 million	$21.1 million (+$1.8M)

Note: *Final number will be based on funding requests from TB/HIV-affected countries.

Sources:
NIH-http://www.hhs.gov/asrt/ob/docbudget/2011budgetinbrief.pdf
GFATM-http://www.pepfar.gov/documents/organization/80161.pdf
Global AIDS-http://www.pepfar.gov/documents/organization/80161.pdf; http://www.oar.nih.gov/budget/pdf/2010_0129_CJ2011.pdf
Domestic AIDS prevention-http://www.hhs.gov/asrt/ob/docbudget/2011budgetinbrief.pdf
Domestic AIDS treatment-http://www.hhs.gov/asrt/ob/docbudget/2011budgetinbrief.pdf
Global TB-http://www.pepfar.gov/documents/organization/80161.pdf
Global TB/HIV-Conversation with staff at the U.S. Office of Global AIDS Coordinator, February 1, 2010
Domestic TB-E-mail exchange with the director of the White House Office of National AIDS Policy, February 1, 2010
Viral Hepatitis-White House FY2011 budget briefing call on domestic AIDS hosted by the White House Office of National AIDS Policy, February 1, 2010

Tools For TB Advocacy

TAG Launches TB Advocacy Toolkit

TAG has launched the first module of the TB Activist Toolkit. This first module, *TB Basics,* provides activists with fundamental information about tuberculosis that can strengthen advocacy and scientific literacy around TB and TB/HIV coinfection. Activists can then use this information to build advocacy plans and to develop community education sessions on TB.

The toolkit includes powerpoint slides that can be customized to meet the needs of activists around the world. Also included are facilitator notes that guide community educators on presentation flow and managing sessions to achieve maximum classroom participation. Facilitator notes are organized around fundamental information, teaching points with optional exercises, reviews of key points for each section, definitions of key terms and nice-to-know information that can enhance the learning experience for learners with varying levels of advocacy and scientific knowledge. Illustrations are provided throughout the course to re-enforce information presented.

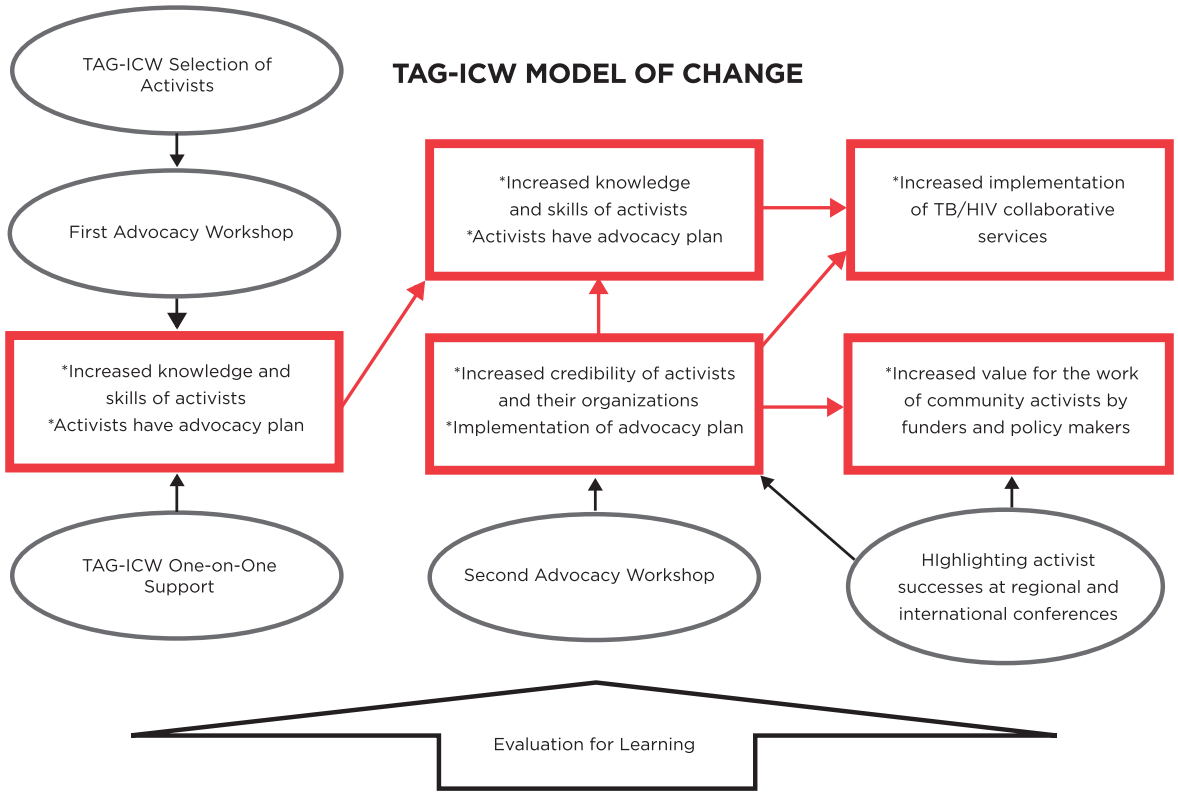
Download this module at *http://www.treatmentactiongroup.org/base.aspx?id=3552*

Upcoming modules include *TB/HIV Epidemiology and Impact* and *TB Treatment.* Check the TAG website regularly for updates.

Empowering Communities for TB Advocacy: The TAG-ICW Model

This publication by TAG and International Community of Women Living with HIV/AIDS (ICW) East Africa, provides activists, policy makers, and donors with lessons learned from two years of capacity building for HIV treatment activists to integrate tuberculosis (TB) and TB/HIV collaborative activities into their advocacy work. The TAG-ICW capacity building model can be used by program implementers, funders, and policy makers to help implement the component of the World Health Organization's (WHO) 2006 TB control strategy that identifies the need to empower TB patients and their communities. Despite its rich history of community mobilization and activism over the past century, in recent decades, broad-based community advocacy for TB care and control efforts have become increasingly rare. TAG and ICW developed this model from our experience building the capacity of Africa-based HIV activists to take on TB advocacy. We strongly believe that the components of the model can be applicable to strengthen TB advocacy globally.

Download this publication at *http://www.treatmentactiongroup.org/publication.aspx?id=3410*



TAG NEW WAYS TO CONTRIBUTE

Supporting TAG is a wise investment in AIDS treatment advocacy. With a small but well-organized and highly respected staff of professionals, every donation to TAG brings us one step closer toward better treatments, a vaccine, and a cure for AIDS. There are several ways you can support TAG today!

Make a tax deductible gift now by credit card using our secure website (www.treatmentactiongroup.org) or by calling Joe McConnell at 212.253.7922 to request a donation envelope.

Celebrate!
Expand your support for TAG by asking your friends and family to make a donation in your honor to celebrate your birthday, anniversary, or the holidays. An acknowledgment will be sent to donors, and you will be informed of gifts made in your honor. Please call Joe McConnell at 212.253.7922 to request that materials be sent to friends and family.

Support TAG's
Research in Action Awards
Each December, TAG's Research in Action Awards event honors some of the most important scientists, artists, celebrities, and activists working for better treatments, a vaccine, and a cure for AIDS. Past honorees and presenters have included New York State Senator Tom Duane, researcher Dr. Trip Gulick, executive director of the Global Fund Michel Kazatchkine, award-winning playwright Terrence McNally, actor David Hyde-Pierce, and stage and screen actress Kathleen Turner, among many other scientists and dedicated AIDS activists. Join us this December!

Does your company have a matching gifts program?
If so, you can double or even triple the donation you make to TAG. If your company offers a matching gifts program, please complete its matching gift form and send it in with your donation to TAG.

Make a gift of stock to TAG
Gifts of stock benefit TAG and the donor. The donor who purchased the stock at a lower price receives the tax deductible benefit of the stock's price on the day it is transferred to TAG.

For more ways to support TAG, please visit our website at www.treatmentactiongroup.org or contact Joe McConnell at 212.253.7922.

TAG BE INVOLVED

About TAG

Treatment Action Group is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS. TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions. TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS.

Program areas include antiretroviral treatments, basic science, vaccines, prevention, hepatitis, and tuberculosis.

Join TAG's Board

TAG is always seeking new board members. If you are looking for a great place to invest your time and talents, please call Barbara Hughes, TAG board president, to learn more about board opportunities with TAG.

Call 212.253.7922 or email:
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