Volume 15, Issue 3, Summer 2008

tagline

TAG
Treatment Action Group

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

Sixteen Radical Steps to End the AIDS Epidemic

From a special plenary session titled "Looking to the Future—The Epidemic in 2031, and New Directions in AIDS Research" at the XVII International AIDS Conference in Mexico City, August 6, 2008

BY MARK HARRINGTON

Twenty years ago this October, fifteen hundred AIDS activists from around the United States surrounded the headquarters of the U.S. Food and Drug Administration in Rockville, Maryland, to demand that it revolutionize its regulatory approach to the testing and approval of new drugs for AIDS. That demonstration was successful beyond our wildest dreams and we are living with its consequences still. Indeed, I and many thousands of others might not be living today had it not been for the unprecedented activism spawned by the AIDS epidemic over two decades ago.

Ten years ago at the Geneva AIDS Conference, mistitled "Bridging the Gap," I was asked to address the question: "Cure: Myth or Reality?" At that time it was evident that the scientific basis for a cure had not yet been established, despite the recent and revolutionary advent of HAART. In Geneva, I called on AIDS activists, community, leadership, and researchers to work to bring HIV treatment along with better prevention programs to the developing countries where most people with AIDS lived and died. Richard Horton summarized the clinical science news of the conference, and he was excoriating in his criticism of the deep divide he witnessed: "This conference was about 'bridging the gap.' So why was it that every day this week, whenever a speaker from a developing world country rose to talk about an issue

central to 'bridging the gap,' seats emptied and the halls began to bleed delegates through the aisles and out into the corridors of the conference centre? I watched this

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happen at least six times to speakers from Africa, India, and Thailand. It was nothing less than shameful…. If you walk out of a room when your own colleagues have travelled long distances…to share their experiences with you: Why should any government bother to listen if you don't…?"

Ten years later we are now all working together—north and south, prevention and treatment, scientists and activists—in an unprecedented global movement that has radically transformed the outlook for millions of people with HIV, saved millions of lives, and prevented millions of HIV infections. We are more unified than we were in 1998. Infighting is less common than it once was. We have some amazing short-term accomplishments to be very proud of. According to UNAIDS, deaths from AIDS might even have started to fall in the last two years.

But these gains are fragile, may be transitory, and may be undermined by forces viral, demographic, and political.

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WHAT'S INSIDE

We must not be lulled into slackening of our efforts. Rather, we must intensify our efforts, and overcome the threats that face us.

What is the state of the epidemic in 2008 and where should we be focusing our efforts?

We must seek a cure and a vaccine because lifelong triple-drug therapy for the currently infected will require 990 million patient years of antiretroviral drugs to be manufactured, delivered, and taken by the already infected 33 million—even if all transmission were somehow magically stopped tomorrow.

Add to this the 2.7 million newly infected each year and over the next 30 years we add another 81 million people who would need lifelong therapy—barring a cure—and this will mean another 2.43 billion patient years of ART.

Accelerating scale-up is the foundation for our coming work. We must scale up faster so that we can put one person on therapy for each new infection. But we need massive investment in research on a cure and on better prevention methods if we are ever going to end the AIDS epidemic. We must strive to continue to lower the numbers newly infected. There are several ways we could dramatically reduce infections rapidly if we are willing to take some radical steps around the world.

1. Universal treatment for women equals universal prevention for infants

We must ensure that every pregnant HIV-positive woman has access to full antiretroviral therapy (ART) from the time her pregnancy is known to when she completes breastfeeding, and then for life if indicated by her CD4 and health status. And we must ensure that every HIV infected baby is diagnosed at birth and treated for life.

2. End gender-based violence and strengthen the legal and health rights of women and sexual minorities

We must demand and achieve equal status for women, gay men, lesbians, bisexuals, and transgender people and end the violence against them everywhere.

3. End the war against sex workers

We must insist on decoupling efforts to stop human trafficking from the current stigmatization and exclusion of sex workers from their full human, health, and economic rights to live and work in dignity, legally and safely.

4. End the war against drug users

We must end the punitive, expensive, and wasteful global war on drug users. We must work in countries around the world to decriminalize possession of drugs; provide universal access to drug substitution therapy, clean syringe exchange, and safe injecting rooms and equipment; and provide services for people reentering society after being unjustly incarcerated for nonviolent drug use.

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5. End health disparities everywhere

HIV rates among black Americans are eight times higher than those of white Americans; 600,000 black Americans are living with HIV and 30,000 new infections occur among them each year. The epidemic among black Americans is the same size as that in Côte d'Ivoire, and bigger than that of seven priority PEPFAR countries put together. The U.S. government and its people are obliged to address this epidemic with the same urgency with which they are now addressing the global pandemic.

The United States must develop and implement a national AIDS strategy with specific targets, timelines, and the goal of reversing the epidemic, with special attention and resources targeted toward black Americans, Latino/Latina Americans, women, and men who have sex with men.

6. Scale up HIV testing and improve HIV epidemiology

We must massively scale up HIV testing globally. New York City has belatedly introduced a policy to test—voluntarily and with opt-out—any resident of the Bronx who presents to the health system. If HIV testing can be massively scaled up in Lesotho, it certainly can and should be massively scaled up in New York City, still the epicenter of the U.S. epidemic.

We must have access to much better, more accurate, and timelier information about where the epidemic is and where it is moving to. Recent revisions downward by UNAIDS on the global pandemic and upward by the CDC on the U.S. epidemic have left the impression that we are still far from having a clear enough picture of the size, scope, distribution, and movement of the epidemic in its 28th year.

7. Define when to start ART

We must continue to accumulate strong evidence about when to start ART. This research is more vital than ever because the public health benefit of scaling up ART depends on maximizing its benefit. For example, starting an appropriate ART regimen earlier for women of childbearing age would likely both benefit the mother and protect the baby.

Given the wealth of information that came from the unexpected results of the randomized SMART study it is urgent that we undertake a long overdue new study of when to start ART.

8. Prevent, diagnose, treat, and cure TB

Everyone has a responsibility to do a much better job of reducing the impact of TB among people with HIV. HIV clinics around the world must implement infection control procedures, intensified TB case finding, and earlier TB diagnosis and treatment so that no one contracts TB while accessing HIV care.

Routine screening for TB at every clinic visit should also allow healthy HIV-positive persons in pre-ART care to receive cotrimoxazole and isoniazid preventive therapies, which despite overwhelming evidence of efficacy are not routinely used in most sites due to overblown fears about resistance, toxicity, and adherence.

9. Develop HIV RNA, CD4, and TB point-of-care diagnostics

We need massive new efforts to develop cheap, accurate, and accessible point-of-care diagnostic tests to measure HIV RNA for infant diagnosis, to measure semiquantitative CD4 counts for disease staging and monitoring ART, and to determine whether someone has active TB disease—either pulmonary or extrapulmonary, among children and adults, whether HIV negative or positive.

10. Diagnose, prevent, and treat viral hepatitis and common opportunistic infections

We should strive to obtain serology and, when possible, treatment for hepatitis B and hepatitis C infections among HIV coinfected persons. Because of the overlapping activity of certain ARV drugs, we are already treating many people who are coinfected with HBV and HIV without knowing their HBV status. As HBV and HCV treatments mature and oral combination therapy becomes possible, we must be ready to scale up hepatitis treatment globally.

Better opportunistic infection prophylaxis and treatment are also needed. Key drugs must be added to the essential medicines formulary and their prices brought down: amphotericin-B for cryptococcosis, azithromycin for MAC and a host of other infections, rifabutin for tuberculosis, and valganciclovir for CMV retinitis.

11. Develop better first-, second-, and third-line antiretroviral (ARV) regimens

We still need cheaper, safer, and more durable first- and second-line ART regimens to guarantee the longest possible duration of viral suppression free of side effects. Though the ART treatment space is maturing, there is still room for better combinations with greater durability, less toxicity, higher barriers to resistance, and cheaper manufacturing costs.

12. Intensify investment in biomedical research, including AIDS research

The last five years have seen stagnation in U.S. investment in research at the National Institutes of Health. The AIDS research budget, nominally $2.9 billion, has lost about 20% of its purchasing power due to inflation during this time. We must demand that the next U.S. president and Congress increase support for all NIH research—including AIDS research—by 15% in each of the next five years.

Other rich countries in the European Union and the Organization for Economic Cooperation and Development must double or triple the amount they invest in biomedical research, including research for AIDS, TB, viral hepatitis, and other diseases. Emerging and developing countries need to increase investment in biomedical research five- to tenfold to help address persistent gaps in health research.

13. Show solidarity with activists, health workers, policy makers, and scientists working on global health issues

We cannot afford a divisive debate that pits advocates for different diseases against each other.

The AIDS movement—made up of activists, scientists, health workers, and policy makers alike—has shown that it is possible to scale up antiretroviral treatment to cover three million people in just five years.

Let's make this the vanguard of an unprecedented global citizens' movement for comprehensive universal primary health care for all. We owe it to our colleagues working in TB; malaria; sexual and reproductive health; maternal and child health; and food security and clean water, among many many others, to unite with them to demand the resources necessary to meet and surpass the millennium development goals and to provide not only universal access to HIV prevention, care, and treatment but universal and comprehensive primary health care for all.

Some will say that this is an impossible aspiration. Some of these naysayers said the same thing about ART scale-up in 2000. Some of them do not want to spend rich countries' resources on global health; some, regrettably, are simply jealous of the success of the AIDS movement in mobilizing resources and making an impact. We cannot afford to descend into quarrels with others who genuinely care about global health.

14. Hold governments accountable to their commitments to health

The 30 richest countries in the world must contribute 0.7% of their GDP to international development. Developing countries must honor their pledge to spend 15% of their national budgets on health. We must reform or abolish the IMF and abolish health user fees, public health sector salary caps, and reduce or abolish burdensome debt. We must commit to spending $50 per person per year on health as recommended by the Commission on Macroeconomics and Health.

15. Reform the World Health Organization

Sweeping institutional reform is also needed at the WHO. Its antiquated constitution makes it accountable only to member countries and not to the citizens of the world. The regional offices for Europe and for Africa are particularly egregious examples of unaccountable bureaucracies consuming millions of dollars while neglecting the health crises at their doorsteps ranging from drug-resistant TB to HIV and many others. Civil society needs to take a role in WHO governance.

16. Stay focused and united

Changes in the global health architecture and in the global political context mean that it will become increasingly difficult to maintain the necessary focus on HIV as it continues to rage unchecked and uncontrolled in a world beset by economic turmoil, famine, global warming, and wars. And some will say that AIDS is no longer an emergency.

We need greater unity

We must become more united if we are to become an even more powerful force for global public health, human rights, and social justice, with our goal of universal access evolving into comprehensive and universal primary care for all. To those who say it cannot be done we must reply, "¡Si se puede! Yes, we can!"

Meet the Activists
Battling the TB/HIV Epidemic through Community Action

Through advocacy workshops and by coordinating and supporting activists' advocacy efforts, TAG and ICW work together to increase community understanding of TB/HIV coinfection and enhance research, treatment, and resources to combat the two epidemics.

Thanks to all of my activist colleagues around the world who impress and amaze me with your work every day.
Nelson Juma Otwoma

Nelson Juma Otwoma, Kenya
Multiface Development and Research Centre


Nelson Juma Otwoma

I have always wanted to make a difference. My activism took root in my home province, Nyanza, Kenya. My activism has always been focused on alleviating the burden of poverty and promoting health. I have always had an intense inner feeling that something needed to change; in fact, I was probably born an activist!

In 2001, I helped to found the Multiface Development and Research Centre (MDRC) with the mission of building local capacity to identify problems and seek suitable solutions in the areas of health and development. In the early days of activism at MDRC, my role was to say the things that no one else was saying…poor people were suffering with disease, poverty, and ignorance. MDRC was well aware of the burden caused by HIV and TB and when the opportunity presented itself, MDRC sought funding to address the burden of TB in the Suba district of Western Kenya. The intention of MDRC was to get people talking about TB and poverty in the hope that TB service delivery would improve in Suba. As the lead researcher of MDRC's TB/HIV Advocacy project, I was able to prioritize TB/HIV as an area of interest for the organization, and this continues to be a cornerstone of my own advocacy agenda.

Through my work with TAG, ICW and other organizations supporting TB/HIV work, I have had the opportunity to learn more about advocacy. I have gained knowledge about research, the skills and steps of advocacy, and the lessons learned from the work done by other activists. This has helped me redefine my own TB/HIV advocacy agenda.

Understanding the science and policy aspects of TB/HIV has been vital in my advocacy to make civil society a stronger partner in allocating resources, as well as making sure that government programs meet our needs. Marrying the understanding of policy, science, and research with my understanding of my community has made the advocacy of MDRC more focused and powerful.

Contact Nelson at otwomatom@yahoo.com.

Aaron Muhinda and Prima Kazoora, Uganda
HEPS-Uganda

HEPS is a health consumers' organization advocating for health rights and responsibilities. Through their involvement with the Advocacy Project, Aaron and Prima have had great success in integrating TB advocacy into HEPS's HIV work. Using resources and knowledge gained from TAG-ICW trainings combined with strong organizational support from HEPS (under the umbrella of the Uganda Coalition for Access to Essential Medicines), they have developed and implemented a TB and HIV medicine and diagnostics monitoring tool. They are using the data on availability and accessibility of TB and HIV medications and diagnostics to lobby policy makers to improve treatment access. This monitoring effort was originally focused on HIV, but participation in the Advocacy Project enabled Aaron and Prima to advocate for the inclusion of TB. HEPS has been able to build strong support for their work by involving diverse stakeholders such as the Ministry of Health, the WHO, and the Uganda AIDS Commission as well as fellow TB/HIV activists and community members.


Aaron Muhinda


Prima Kazoora

For more information, please visit www.heps.org or e-mail Aaron at muhindaaaron@yahoo.com or Prima at pmkazoora@yahoo.com.

The unique challenges presented by TB/HIV coinfection should be a focus for HIV activists worldwide. Even though TB is curable:

- TB kills nearly 1.5 million people a year, of which 250,000 are people with HIV
- TB is a disease of poverty, with 98% of TB deaths occurring in developing countries
- Africa has 80% of the world's TB/HIV burden despite being only 13% of the world's population
- TB is the leading cause of death among people with HIV (15% of deaths due to TB globally and up to 50% in some parts of sub-Saharan Africa)

About the TB/HIV Advocacy Project

Treatment Action Group (TAG) is a U.S.-based independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS. The International Community of Women Living With HIV–East Africa (ICW) is based in Kampala, Uganda, and is the only international network run for and by HIV-positive women. It was founded in response to the desperate lack of support, information, and services available to HIV-positive women worldwide and their need for influence and input on policy development.

The TB/HIV Advocacy Project strengthens the capacity of communities affected by HIV/AIDS to understand, mobilize, and respond effectively to the challenges posed by the intersecting TB and HIV epidemics.

The TAG-ICW Advocacy Project is part of TAG's broader TB/HIV Project, which has the following objectives:

- strengthening the advocacy efforts of Africa-based HIV organizations to improve access to TB/HIV collaborative services
- working with global TB/HIV advocates to ensure that global program and funding efforts are informed by and reflect the priorities of persons living with TB/HIV
- creating awareness of TB/HIV issues among the U.S. political leadership to increase national support for TB threefold
- engaging with TB research and development initiatives, both public and private, to ensure that they are well resourced and working with community input to develop tools that are critical to address the TB/HIV epidemic

As part of their joint effort to support and coordinate increased TB/HIV advocacy, TAG and ICW have worked closely with over 40 activists from 25 different countries. Since September 2007, TAG and ICW have provided three, multiday advocacy workshops and sponsored a daylong satellite session at the Union Conference on Lung Health for selected TB/HIV activists. The first two workshops, held in Kampala and Abidjan, focused on providing essential TB/HIV knowledge in the areas of basic science, diagnostics, treatment, research, and advocacy to Anglophone and Francophone activists, respectively. The third workshop, in Addis Ababa, brought together all of these activists and provided updated technical and policy information as well as skills-building sessions based on advocacy targets prioritized by the activists (TB/HIV implementation, research, media, and Africa Union/UNGASS).

The workshops have created opportunities for activists to support each other and gain a broader perspective of the global struggle to fight TB and HIV.

Carol Nawina Nyirenda, Zambia Treatment Advocacy and Literacy Campaign (TALC)

Carol has lived with HIV for many years and has also survived TB treatment. She has been able to transform this personal experience into a political campaign to address TB/HIV, and has incorporated TB advocacy into her national and global HIV activism.

Participating in the TAG-ICW advocacy trainings gave Carol a knowledge base of TB science, diagnostics, and treatment that has enabled her to train other activists on TB and TB/HIV coinfection and, along with fellow Zambian activists, to advocate for the Zambian government to implement WHO recommendations for collaborative TB/HIV activities. Carol has received global recognition for her activism and served as a panelist at the April 2008 meeting in Thailand of the UNAIDS Program Coordinating Board (PCB), addressing the issue of multidrug-resistant TB among people living with HIV. In part, her advocacy led the UNAIDS PCB to decide to monitor TB/HIV mortality numbers as a measure of the impact of the implementation of the collaborative activities recommended by the WHO policy to reduce the burden of TB/HIV. Carol was also invited to be part of the International Treatment Preparedness Coalition's World CAB meeting to discuss treatment access issues with the pharmaceutical industry. She is a community representative on the Stop TB Partnership's New Diagnostics Working Group, and is a board member representing communities of people living with TB, HIV, and malaria for UNITAID, where she has successfully lobbied for the provision of resources for diagnostics for TB drug resistance testing. For more information, please visit www.talczambia.org or e-mail Carol at carolnawina@yahoo.com.

Carol Nawina Nyirenda

Coulibaly Gaoussou, Cote d'Ivoire Bouake Eveil

Coulibaly has been very active in advocating for the implementation of TB/HIV collaborative activities in his country. Through his work with Bouake Eveil, Coulibaly has provided support and education to people living with HIV and those who are coinfected, with a particular focus on the importance of TB preventive therapy among people living with HIV. His organization has successfully advocated for a more collaborative approach to fighting TB and HIV in the Bouake district and Coulibaly has also participated in some national HIV policy discussions and pushed for the inclusion of TB/HIV. Coulibaly has developed a comprehensive TB/HIV program in his organization that includes infection control measures and community TB/

Coulibaly Gaoussou

HIV sensitization. He has also created an association of people living with HIV and TB and their families. Because Bouake is affected by rebel activity, public health services are unstable, so Coulibaly also makes home visits to persons with HIV and TB to ensure that people have access to needed services. For more information, please e-mail Coulibaly at c_gaoussou@yahoo.fr.

Joel Mayowa, Nigeria
Treatment Access Movement;
Obatunde Oladapo, Nigeria
Positive Life Association of Nigeria;
Stop TB Partnership-Nigeria

In November 2007, Joel and Oba traveled to the Union World Conference on Lung Health in Cape Town, South Africa, as part of their participation in the Advocacy Project. At the conference they met with other Nigerian stakeholders who were dismayed by their country's dismal level of participation in the conference as well as the lack of a coordinated response to address the TB burden in Nigeria. As community representatives to the Stop TB Partnership Working Groups on TB/HIV (Oba) and Advocacy, Communication, and Social Mobilization (Joel), they advocated for the creation of the Stop TB Partnership–Nigeria. This goal was achieved in May 2008 when over 90 national stakeholders gathered for the group's inaugural meeting. Joel and Oba are helping to plan the first Nigerian National TB Conference to increase awareness of persons with HIV about the importance of TB/HIV. They have also done capacity building on TB/HIV treatment literacy and advocacy for different stakeholders in the country, including government, NGOs, and people infected and affected by either or both TB and HIV. Both Joel and Oba have stated that the TAG-ICW Advocacy Project, which provided them with treatment and policy literacy and advocacy workshops, has helped them be more effective TB/HIV activists. For more information, please email Joel at mayowajoel@yahoo.com or Oba at obatunde65@gmail.com.

Obatunde Oladapo

Joel Mayowa

Wim Vandevelde, Portugal
European AIDS Treatment Group

Before participating in the Advocacy Project, Wim's main focus was HIV/HCV treatment advocacy for countries in the WHO European region. TAG-ICW training and support provided Wim with the tools to understand why TB is of concern for persons with HIV and strengthened his capacity to incorporate TB into his advocacy work. Wim was invited to be part of the Advocacy Project because of his role as a community representative to the Stop TB Partnership's New Drugs Working Group. He has also helped to set up a civil society network of Lusophone countries where he successfully advocated for the inclusion of TB/HIV into the network's priorities as well as into the Community of Portuguese Language Countries' health agenda. Wim gave a keynote address on community input in the regulatory process at the Global Alliance for TB Drug Development's Open Forum meeting in New Delhi in May 2008, ensured the inclusion of community perspectives in a scientific paper on priorities for new TB drug development, and provided the community perspective to the Portugal Ministry of Health on World TB Day. As chairperson of the EATG, Wim often meets with the private sector to monitor and advocate for a drug research agenda that responds to community priorities, and since his involvement with TAG and ICW Wim has incorporated TB drug development concerns in his meetings with pharmaceutical companies. For more information, please visit www.eatg.org or email Wim at wim@eatg.org.

The workshops have created opportunities for activists to support each other and gain a broader perspective of the global struggle to fight TB and HIV.

Wim Vandevelde

Thembi Nkambule, Swaziland
Swaziland National Network of People Living with HIV/AIDS

As an HIV treatment activist in a country with high TB/HIV prevalence, Thembi welcomed the opportunity to learn more about TB and to incorporate this knowledge into her activism. After attending advocacy workshops Thembi, through SWANNEPHA, has provided training on TB/HIV to 38 support groups and a core group of activists, and has improved SWANNEPHA's capacity to do TB/HIV advocacy and outreach. She has also helped develop a community training manual on TB/HIV and has already seen more comfort on the part of people with HIV to discuss TB within their network. Thembi has also been working on national policy advocacy to get people with HIV meaningfully integrated into TB and HIV programming and service delivery. Her national work was shared with global activists and TB/HIV implementers when she presented findings from her own and other activists' work at the 2008 PEPFAR HIV/AIDS Implementers Meeting in Uganda in June 2008. For more information, e-mail Thembi at tnkambule@swannepha.org.sz.

Thembi Nkambule

Notes on the 2008 International AIDS Conference

The struggle for social justice is deeply woven into the fight against AIDS—and will likely continue long after AIDS has faded.

BY BOB HUFF

At the XVII International AIDS Conference, held in Mexico City this summer, a new drama debuted over the long-term direction of the fight against AIDS. The battle is portrayed in the health policy arena as vertical programs that treat HIV in isolation from the general health environment pitted against horizontal programs that seek to strengthen countries' overall health systems. But the real struggle may be over how the vast amounts of money now given for AIDS relief are channeled, with vertical money going to health ministries, NGOs, and programs, and horizontal money going directly to central treasuries. Obviously, those holding power in governments prefer the latter, while AIDS activists say it would be foolish to abandon a plan that is working, and that a "diagonal" approach to extend the success in AIDS to the rest of society is a better idea. But the issue may no longer be what is best for health. With annual AIDS dollars now in the tens of billions and climbing, powerful interests may be encroaching on health policy as the money increasingly looks like "foreign aid," which has historically been used to buy influence and gain hegemony in the political world.

At past conferences, battles were fought over prevention versus treatment as public health experts debated which approach should have precedence in controlling the AIDS pandemic. With treatment now proven successful and PEPFAR funding secure for a few more years, prevention joined treatment on the stage in Mexico without crowding, and the time seemed right for a grand alliance. Treatment reduces fear and stigma and increases the likelihood of testing. It reduces viral load and the likelihood of transmitting HIV. And treatment is becoming a cornerstone of prevention now that expectations for technology have been cooled by setbacks in vaccine and microbicide research. Meanwhile, proven prevention interventions like circumcision have been slow to take off and promising preexposure prophylaxis trials stumble forward. The field is overdue for a renaissance in behavioral prevention research, which had been severely limited by funding restrictions during the U.S. conservative surge of the past eight years.

Human rights and the visibility of marginalized behaviors (sex work, homosexuality, and drug use) were central to this conference. The organizers deliberately shift focus every two years to bring contentious and previously underrepresented perspectives into the foreground, though some attendees complained that emphasis on women and on the African epidemic had been shuttled from the stage too soon. A new realism about "risk" behaviors was also evident, with a growing understanding that there are underlying emotional dimensions to what people do and prevention approaches that address rational choice alone fail to have lasting impact.

With release of the CDC's increased U.S. HIV incidence estimate, attention also turned to prevention in the United States. There was something disingenuous about the alarm expressed over the 40% higher number, however, as if the old estimate of 40,000 new infections per year did not warrant a determined response. Yet during the Bush administration—when serious prevention research addressing sex workers, MSM, drug users, and gay youth was essentially taboo—the prevention infrastructure became fractured and progress stopped. Frustrated by restrictions and a climate of fear, much of the creative and energetic prevention talent drifted away from AIDS service organizations, leaving prevention programs in the hands of administrators and timid leaders where they languished.

If one steps back from the medical aspects of AIDS just a little, the vast background of social injustice is not hard to see. In Mexico, social issues were discussed with much less abstraction and greater realism than at prior conferences. On the legal and human rights fronts, the threats of criminalization were in the spotlight and there was recognition that social change does not always move in a progressive direction. So-called model laws that punish transmission of HIV are spreading in Africa and elsewhere. These laws threaten to increase stigma and inhibit testing and treatment, while visiting unjust and disproportionate retribution on a few, highly vulnerable individuals. Criminalization only seems rational in an environment of ignorance and fear and must be opposed with plain-speaking leadership at the highest levels.

A revolution in culture and society cannot be counted upon to solve the HIV crisis, however, and this is why interest in the medical and scientific progress continues to overshadow the attention and money given to social and behavioral interventions. Transformations caused by ideas alone are rare in history, but revolutions introduced by technology are common—and cultural changes follow in their wake. Effective new technologies like gunpowder, penicillin or cell phones, whether destructive, lifesaving or merely convenient, spread quickly and tend to erase the memory of what life was like before their appearance. For AIDS, a single, cheap, nontoxic, and highly effective antiretroviral pill would make achieving universal access to HIV treatment much more likely. An effective, one-shot, preventive vaccine could, over time, reduce the HIV conflagration to smoldering embers, removed from the public consciousness, much as polio is today.

The XVII International AIDS Conference in Mexico City may have displayed a more mature understanding of the social dimensions of HIV, but the struggle to incrementally improve the lives of the millions affected will be slow, even if a transforming HIV technology emerges. Unfortunately, no such technology was revealed in Mexico City.

The Shrinking of PAVE100
Large-Scale Vaccine Trial Nixed

NIAID's announcement that it would not support the 2,400-person PAVE100 trial left open the possibility of an even smaller trial, solely evaluating the impact on postinfection viral load set point.

BY RICHARD JEFFERYS

A little over a year ago, the HIV vaccine field was shaken by the news that Merck's adenovirus serotype 5 (Ad5)-based candidate had failed to protect against HIV infection or lower viral load among recipients who became infected. Even worse, the vaccine appeared to increase susceptibility to HIV infection among a subset of trial participants with preexisting antibody responses to Ad5 (see *TAGLine* 15, no. 1). At the time these results were announced, the National Institutes of Health (NIH) was gearing up to launch a large, international, 8,500-person efficacy trial of another Ad5-based HIV vaccine candidate designed at the NIH's Vaccine Research Center (VRC); inevitably this study—dubbed PAVE100—was put on hold as scientists trawled through the data from the Merck vaccine trial to try and better understand what happened. After a series of meetings, consultations, and finally an executive decision from Anthony Fauci (director of the National Institutes of Allergy and Infectious Diseases at NIH), PAVE100 is now being redesigned as HVTN 505: a small, U.S.-based "test of concept" trial that will involve around 1,400 people.

Thinking Big

The original design of PAVE100 was intended to provide a robust answer regarding the protective efficacy of the VRC vaccine candidate, and to also provide data that—in combination with the results from the Merck vaccine trial—would help guide future HIV vaccine research. The VRC approach involves a series of initial immunizations with a DNA priming vaccine followed by a single shot of an Ad5 vector. This is significantly different from Merck's Ad5-only strategy. The VRC vaccines also contain additional HIV antigens: the envelope proteins from three different HIV-1 clades (A, B, and C) are included along with the Gag, Pol, and Nef proteins that were also in the Merck construct. It was hoped that the results from trials of the two vaccines would show if these differences impacted protective efficacy. However, when it emerged that

The original design of PAVE100 was intended to provide a robust answer regarding the protective efficacy of the VRC vaccine candidate.

Merck's Ad5 vector had not only failed show any efficacy but was also associated with an increased risk of HIV infection among participants with anti-Ad5 antibodies, it quickly became obvious that PAVE100 could not proceed as originally designed. The trial population was focused on Southern Africa, where the vast majority of individuals (~80%) have antibodies against Ad5, and the potential for the VRC's vector to have a similarly adverse impact on susceptibility could not be ruled out.

In Committee

The task of mulling whether PAVE100 could be redesigned in a way that would allow the efficacy of the VRC vaccines to be safely studied fell to a NIAID advisory body called the AIDS Vaccine Research Subcommittee (AVRS, formerly known as the AIDS Vaccine Research Working Group). At a meeting on December 12, 2007, AVRS members listened to presentations on the Merck results and the PAVE100 design and offered a series of recommendations to the PAVE100 protocol team, led by principle investigator (PI) Scott Hammer. The recommendations included reducing the sample size and focusing on a single population, as well as excluding individuals with Ad5 antibodies and uncircumcised men (because analyses of the Merck results indicated that circumcision protects against the enhancement effect observed in the trial). The PAVE100 protocol team then spent several months designing a new trial called PAVE100A, incorporating all the AVRS recommendations and ending up with a proposal for a 2,400-person, U.S.-based trial that would enroll only circumcised gay men lacking anti-Ad5 antibodies. The co-primary endpoints were slated to be a lack of enhancement of HIV acquisition (e.g., confirming the safety of the Ad5 vector in this population) and a reduction in set point viral load among vaccine recipients who became infected. Multiple secondary immunological analyses were also included in the hopes of maximizing what could be learned from the study, particularly in terms of looking for correlations with either prevention of HIV infection or control of postinfection viral load.

The proposal for PAVE100A was formally presented by Scott Hammer at a specially convened meeting of the AVRS that took place on May 30, 2008. TAG released a statement to coincide with the event, noting that the decision was a "tough call" and outlining TAG's view that the safety cloud hanging over Ad5 vectors and the inability of the VRC vaccine to induce broader responses to the HIV Gag protein than Merck's argued against conducting PAVE100A. The AVRS meeting was presided over by Anthony Fauci, who explained that the final decision on whether to move forward with the trial rested solely on him. AVRS members also heard the latest news from ongoing analyses of the Merck trial data. Julie McElrath presented immunological analyses showing an inverse correlation between the magnitude of the Gag-specific CD8 T-cell response induced by Merck's vaccine and the set point viral load in the subset of trial participants lacking anti-Ad5 antibodies;

the numbers were small, however, and the statistical significance fragile. The majority of AVRS members ended up voting in favor of conducting PAVE100A, but a variety of different and sometimes mutually incompatible reasons were offered in justification. Some members felt that the VRC vaccine was sufficiently different from Merck's that it stood a better chance of working. Among the differences cited were better CD4 T cell responses, the inclusion of envelope antigens and possible induction of envelope-binding antibodies, and potentially more functional CD4 and CD8 T-cell responses due to the DNA/Ad5 prime-boost approach. Conversely, other AVRS members supported PAVE100A on the basis that the VRC's vaccine was sufficiently similar to Merck's that it might be able to confirm the associations between vaccine-induced T-cell responses and postinfection viral load levels that McElrath had described at the meeting.

Executive Decision

Several weeks after the AVRS meeting, Anthony Fauci announced that NIAID had decided not to conduct PAVE100A. However, NIAID's announcement left open the possibility of an even smaller trial of the VRC vaccine, solely evaluating the impact on postinfection viral load set point. This type of trial has been proposed by the International AIDS Vaccine Initiative (IAVI) and dubbed a "screening test-of-concept" for T-cell-based vaccines. Once again, the PAVE100/100A protocol team and PI Scott Hammer—who, it is probably fair to say, have not been well-served by the extended and rather muddy decision-making process surrounding the trial—are having to go back to the drawing board. In the last few weeks, NIAID's vaccine communications staff has announced that a 1,400-person trial (now designated HVTN 505) is in the works, involving the same population proposed for PAVE100A: U.S. based men who have sex with men who are circumcised and lack anti-Ad5 antibodies. NIAID is beginning a series of consultations with stakeholders in the trial, including community-based organizations. More details are expected to emerge as a formal protocol for the study is developed. The trial is not expected to begin until sometime in 2009.

Individuals and community-based organizations interested in participating in the HVTN 505 consultation process can join the AIDS Vaccine Advocacy Coalition's Advocates Network: www.avac.org

A Chimpanzee Tale
Why Are They Resistant to AIDS?

Since the 1980s it has been documented that chimpanzees infected with HIV in research studies typically control viral replication and remain asymptomatic. In only a few reported cases have infected chimpanzees developed persistent immune activation, CD4 T cell loss and opportunistic infections characteristic of AIDS.

BY RICHARD JEFFERYS

Since the 1980s it has been documented that chimpanzees infected with HIV in research studies typically control viral replication and remain asymptomatic. In only a few reported cases have infected chimpanzees developed persistent immune activation, CD4 T-cell loss and opportunistic infections characteristic of AIDS. The reasons for the different outcomes between human and chimpanzee HIV infections have been the subject of much theorizing and even controversy. The discovery that chimpanzees are the source of HIV's closest antecedent, a virus called SIVcpz, led some scientists to hypothesize that chimpanzees alive today may be the descendants of those animals who were able to control SIVcpz and ward off immunodeficiency sometime in the past when SIVcpz first entered the chimpanzee population. In other words, present-day chimpanzees are the survivors of an AIDS epidemic that killed susceptible SIV-infected animals.

In 2002, a paper published by Natasja de Groot and colleagues offered some inferential evidence for this hypothesis. The paper showed that particular immune response genes are common among chimpanzees while others are rare, indicating that something in the past favored the survival of chimps possessing the now common genes. The genes in question are called class I major histocompatibility (MHC) genes and they make the receptors used by CD8 T cells to recognize pathogen-infected cells (once recognized, CD8 T cells can then kill the infected cell). There are many different class I MHC gene variants, which in turn make CD8 T-cell receptors that vary in the efficiency with which they can bind to and recognize the fragments of pathogens (called epitopes) that are displayed (as a sort of alarm signal) by infected cells. The authors of this paper speculated that the class I MHC genes that make CD8 T-cell receptors capable of efficient recognition of SIVcpz-infected cells were those that had been selected for in the present-day chimpanzee population. This theory would explain why most chimps are able to exert strict immune control over the very similar virus, HIV-1.

In a recent issue of the journal *AIDS*, a group of researchers led by Ilka Hoof from the Technical University of Denmark presented data that offers new and compelling support for this idea. MHC genes in humans are called Human Leukocyte Antigen (HLA) genes and there is now a vast literature

demonstrating that certain class I HLA genes are strongly associated with long-term nonprogression of HIV infection and control of viral replication to less than 50 copies in the absence of any treatment (sometimes called "elite control"). Among the strongest associations are with the HLA genes designated B*57 and B*27, which are significantly and consistently overrepresented in cohorts of long-term nonprogressors and elite controllers. These HLA genes have also been shown to make CD8 T-cell receptors that are particularly good at recognizing a broad array of HIV epitopes, rendering CD8 T cells very efficient at recognizing HIV-infected cells. The researchers decided to investigate whether there are similarities between the HLA genes associated with control of HIV in humans and the MHC genes now common among chimpanzees. What they found is that the CD8 T-cell receptors encoded by the human HLA genes are structurally very similar to those encoded by chimpanzee MHC genes. In both cases, the receptors are capable of recognizing a particularly broad range of different epitopes from the Gag protein of SIV and HIV. These data strongly suggest that chimpanzees today are descended from the long-term nonprogressors of a past chimpanzee SIVcpz epidemic, and that the conundrum of chimpanzee resistance to AIDS may finally be solved.

Another implication of the research is that if HIV were to spread uncontrolled through the human population, the HLA genes associated with nonprogression would become more common and, as a result, immunological control of HIV replication would become the norm rather than the exception. Thankfully, however, this harsh Darwinian scenario can be avoided with effective treatment and prevention.

It remains uncertain if the findings can assist efforts to develop an effective HIV vaccine; on the one hand, they add to the evidence that CD8 T cells play a crucial role in controlling viral replication but, on the other, it is unclear if vaccination can increase the efficiency of the CD8 T-cell response in people lacking favorable HLA genes. In terms of vaccine targets, the data echo other recent studies indicating that broad responses to the HIV Gag protein are an important correlate of immune control but, again, the ability to induce broad responses to Gag with a vaccine may be dependent on an individual's HLA genes. Ongoing efforts to enhance and broaden T-cell responses to HIV vaccines should help resolve these uncertainties.

Hoof, I, Kesmir, C, Lund, O, Nielsen, M. Humans with chimpanzee-like major histocompatibility complex-specificities control HIV-1 infection. AIDS 22;11:1299-1303

de Groot NG, Otting N, Doxiadis GG, et al. Evidence for an ancient selective sweep in the MHC class I gene repertoire of chimpanzees. Proc Natl Acad Sci USA 99;18:11748-53

What's in the Pipeline?
Introduction to the TAG Report

TAG's *2008 Pipeline Report* was released at the XVII International AIDS Conference in Mexico City in August. This is the introduction to that report.

BY BOB HUFF

Treatment Action Group's annual pipeline report is a review of medical technologies that stand a good chance of benefiting people with HIV within the next few years. It also covers those that may take longer to develop but represent innovation within the field.

This year our report has expanded to cover treatment and preventive vaccines for the hepatitis B virus and diagnostics for tuberculosis. These are natural extensions to our updates on HIV antiretroviral treatment, hepatitis C treatment, drugs and vaccines to treat and prevent tuberculosis, immune-based therapies for HIV, and HIV prevention technologies, including vaccines and microbicides.

In some areas, such as treatment for hepatitis C virus (HCV), the therapy pipeline is bubbling, with over 20 drugs listed in middle to late stages of development. Despite all the activity, no single drug is likely to revolutionize the current, difficult HCV treatment paradigm, though shortened treatment durations and increased rates of successful outcomes may begin to benefit people with HCV within the next few years. Unfortunately, people with HIV are often unnecessarily excluded from HCV research.

Tuberculosis (TB) is treatable and curable, yet it remains the top killer of people with HIV worldwide. A major limitation to broader and more effective TB treatment in the developing world is the lack of a simple and reliable means of diagnosis—and TB is especially hard to diagnose and treat in people with HIV. Hampered by limited investment in the field, the TB diagnostic pipeline mainly contains advances aimed at high-tech national laboratories or adaptations of existing technology that can be used in regional hospitals. There is much less on the horizon for TB diagnostics that can be used in rural settings, where the need is greatest.

TB drug therapy is also undergoing a period of renewed activity after decades of stasis. Five novel TB drugs are in clinical trials, and funding to explore improved treatment strategies with existing drugs has increased, though it lags far behind the need—especially in light of the growing problem of drug-resistant TB. As with HCV, the near-term goals for TB therapy are to reduce treatment times and improve success rates. Better TB treatment options for people with HIV are also a high priority. Improved TB preventive vaccines offer the promise of cost-effective, wide-scale

reductions in future cases of TB, though their impact may be decades away. A few candidates are in human trials, but many questions remain. One obstacle to getting the answers is the uncertainty of future funding for large-scale clinical trials of TB vaccines.

After a flurry of new drug approvals in the past year, the HIV treatment pipeline is slowing. Most gains in antiretroviral therapy over the next several years will likely come from treatment strategy refinements that build on recently approved drugs. Agents in the pipeline are generally expected to offer incremental, yet important, improvements over existing products. With interest in HIV drug research maturing, the field is ready for investment in a conceptual leap to discover radically new therapies that disable or even cure HIV infection, perhaps by unleashing innate mechanisms of anti-HIV immunity that the virus currently evades. Interest in developing new treatments to control or eradicate hepatitis B virus (HBV) is slowly increasing, but the field is restricted by gaps in the scientific understanding of the virus. Current treatments—mostly spin-offs from HIV drug research—suppress HBV but, as with HIV, are vulnerable to the emergence of drug resistance. Exploration of strategies to prevent resistance, possibly through combination therapy, is the next frontier for HBV, with novel drugs much farther down the road.

The failure of two leading experimental agents in HIV prevention technologies has created a gloomy outlook for this field, though research is generally well funded and continues apace. An unexpected increase in HIV infections associated with a leading HIV vaccine candidate has stimulated a wrenching reappraisal of research priorities. With much greater understanding of the basic science of HIV needed, it may be said that the HIV vaccine field remains in a toddler state. Yet because no other intervention promises so much for future control of the epidemic, support for HIV vaccine research remains strong. The vaginal microbicide field also saw a leading candidate fail in a late-stage clinical trial. Other, likely stronger, microbicide candidates, are at earlier stages of development.

Research on therapies or vaccines to strengthen or stimulate the adaptive immune system to fight HIV remains the poor stepchild to drug and preventive vaccine science. Immune-based therapy research is closely associated with the scientific investigation of how HIV causes disease, and increased investment in this field may pay off in ways that are not immediately foreseeable. Agents in this pipeline tend to be earlier in development but represent a great variety of experimental and innovative approaches.

Research on new technologies to prevent, treat, and diagnose HIV and its coinfections is progressing in 2008. Some fields, such as HCV, are full of activity as drug sponsors race to be first in the market with a transformative therapy. Hepatitis B research may be the next field to get the attention of the commercial sector. Other fields, such as TB research, appear active because they are catching up after years of neglect, though the gap in the needed investment remains large. Antiretroviral research has made dramatic progress over the past 13 years, but seems to be entering a slow phase as recent advances are consolidated into the standard of care. For over 20 years, a preventive HIV vaccine has seemed perpetually just out of reach, though setbacks like the field has just experienced can create opportunities for new ideas to emerge.

Overall, the 2008 HIV pipeline suggests progress and hope. TAG's 2008 Pipeline Report reveals not only the current status of these technologies but also underscores the need for continued and greater investment in making them useful and widely available.

From TAG's 2008 Pipeline Report: Antiretroviral Drugs in Development

Agent	Class	Sponsor	Status
Rilpivirine (TMC278)	NNRTI	Tibotec	Phase III
Vicriviroc	CCR5 antagonist	Schering	Phase III
Elvitegravir	Integrase inhibitor	Gilead	Phase III
Bevirimat	Maturation inhibitor	Panacos	Phase II
TNX-355	CD4 blocker	Genentech	Phase II
Apricitabine	NRTI	Avexa	Phase II/III
Amdoxovir	NRTI	RFS Pharma	Phase II

Antiretroviral Drugs: Development Suspended or Discontinued

Agent	Class	Sponsor	Status
AMD11070	CXCR4 blocker	Anormed	Suspended
BMS378806	gp120 blocker	BMS	Discontinued
INCB9741	CCR5 blocker	Incyte	Discontinued
KP-1451	Viral decay accelerator	Koronis	Suspended

Copies of the entire 2008 Pipeline Report *can be obtained at www.treatmentactiongroup.org*

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 web site (www.treatmentactiongroup.org) or by calling Joe McConnell at TAG 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 the donor, as well as to you informing you of the gift made in your honor. Please call TAG 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, director and artist John Waters, award-winning playwright Terrence McNally, actor Nathan Lane, 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 TAG 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: barbara.hughes@treatmentactiongroup.org

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