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The routine HIV testing model first adopted in some African countries is now being recommended in the US in an effort to finally reduce the spread of HIV

By Kristen Jill Kresge

Only a few years ago Botswana had one of the highest HIV prevalence rates in the world. In 2002 the government started a national treatment program to provide free antiretrovirals (ARVs) to all HIV-infected individuals in need, but very few people were benefiting. By 2004 only 17,500 of the estimated 110,000 people in need—a mere 16%—were receiving treatment. The reason for the poor uptake was that most people didn't even know they were infected with HIV (*PLoS Med.* **3**, 7, 2006).

Researchers have observed that the number of people willing to undergo HIV testing is higher when treatment programs are available. This stands to reason since without life-saving medicines an HIV/AIDS diagnosis is, for most people, the notification of an early death. Fortunately, as ARVs are increasingly available in developing countries, more and more people are being tested for HIV infection. In South Africa the number of people undergoing voluntary counseling and testing (VCT) doubled between 2004 and 2005 when the government's treatment program was introduced. Other African countries, including Lesotho and Malawi, are also expanding their VCT efforts.

But in Botswana this "if you build it, they will come" treatment and testing scenario did not seem to be working. Despite a national treatment program, only 70,000 HIV tests were performed in a country of 1.7 million people through mid-2003. In response President Festus Gontebanye launched a routine HIV testing initiative in January 2004 that meant everyone seeking healthcare received an HIV test unless they specifically refused.

There was hope this approach would encourage more people to be tested by erasing some of the stigma associated with the disease, which is one of the main barriers to HIV testing in developing countries. Making testing more commonplace also helps prepare communities for HIV prevention trials, like those for vaccines and microbicides, where volunteers must first be screened for HIV infection.

In Botswana, more testing also meant healthcare workers could link HIV-infected individuals in need to the national treatment program. In just two years this initiative spurred

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Stemming the flow

Health worker brain drain to industrialized nations has been receiving attention, but less often discussed is the depletion of developing country research talent

By Sheri Fink

Several years ago, Dr. Veronica Mulenga, a Zambian physician, was offered a two-year research training fellowship at Miami University. She gained her research skills in well-run, state of the art facilities. The situation when she returned home was markedly different. "A lack of equipment, erratic supplies of reagents, even drugs," says Mulenga, now a consultant pediatrician at the University Teaching Hospital in Lusaka, where she conducts clinical research on critically important treatment parameters in HIV-infected children. While Mulenga has toughed it out in less-than-ideal conditions, she says many of her colleagues have made a different decision: they are no longer working in the country. "They become frustrated with the systems they come back to—poor administration, poor objectives," she says. "Quite a lot of people return and then leave again because of frustration."

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significant progress and Shelia Tlou, the country's health minister, reports that now 70% of those who need ARVs are receiving them from the government. Studies also indicate that routine testing is widely supported by the citizens of Botswana (*PLoS Med.* **3**, 261, 2006).

This dramatic turnaround was hailed as a great achievement by public health experts and many started touting Botswana as a model for other African countries. The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) modified their HIV testing guidelines to recommend that other countries with high HIV infection rates follow Botswana's lead.

Now a similar routine testing paradigm for HIV, known as opt-out testing, is also being recommended by the Centers for Disease Control and Prevention (CDC) in the US, where it is estimated a quarter of a million people are currently HIV infected and don't know it (*MMWR Recomm. Rep.* **55**, 1, 2006). This major shift away from the VCT model that was created for HIV has provoked both praise and criticism, but more than anything it has raised many questions. "We're pleased to see that there's been a lot of open dialogue about this," says Bernard Branson of the Division of HIV/AIDS Prevention at the CDC.

Everyone agrees that conducting more HIV testing will have many benefits, the most obvious of which is identifying those who are HIV infected and promptly referring them to treatment and care services. Most researchers also concur that people who know their HIV status will be more likely to change their behaviors to protect either their partners or themselves from future infection. Such behavioral modification should result in fewer new infections. But many researchers, clinicians, and activists are carefully considering the legal and human rights issues involved in routine testing, the use of HIV prevention counseling, and whether there is enough money and manpower to ensure that the HIV-infected individuals identified through widespread testing will be connected with treatment programs. "We have to measure our success not just on the number of tests or diagnoses, but on how many people receive care and treatment," says Jeffrey Levi, executive director of the public policy association, Trust for America's Health.

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Jeffrey Levi

Success stories

Botswana's routine testing program was not the first of its kind. The model was adopted much earlier in the HIV epidemic by many developed countries—including several states in the US—as a way to identify HIV-infected pregnant women. This initiative has resulted in more women being placed on treatment during pregnancy and has helped dramatically lower the number of HIV-infected infants born in developed countries.

There is also evidence from some testing initiatives in the US, adopted on a state-by-state basis, that routine testing is an effective way to eliminate barriers to HIV testing. New York City started an HIV testing initiative in public hospitals that serve 1.3 million people in the metropolitan area that increased testing rates by 57% and doubled the number of new HIV diagnoses. Similar initiatives have also occurred in Texas and Colorado.

Washington, DC also launched a new testing campaign in June called 'Come together DC, get screened for HIV' that included several initiatives to expand access to testing, with plans to eventually make it routine in all healthcare settings. Marsha Martin, senior director of HIV/AIDS administration for the district's department of health, calls routine testing "the best of public health." As of September this program has tested more than 16,000 people for HIV, a 300% increase over the previous year.

Taking action

Over the past two years the number of people with AIDS has increased in every region of the world, according to the annual report on the global epidemic issued in December by UNAIDS and WHO (www.unaids.org/en/HIV_data/epi2006/). In the US there are still 40,000 people newly infected with HIV each year and, despite sustained HIV prevention efforts and public health campaigns, the number of new infections has not declined at all over the past 15 years.

Moreover many of these new infections are being discovered late—40% of people in the US progress to AIDS within a year after discovering they are infected with HIV. The progression from initial infection to an AIDS diagnosis typically takes about a decade, so it is possible that these people are transmitting HIV to others for many years unknowingly.

Mike Saag is a professor of medicine at the University of Alabama in Birmingham

Jean-Marc Giboux/Getty Images

Vials of blood collected for HIV testing. Samples are bar coded to protect the anonymity of the individuals being tested.

HIV testing is more cost effective than testing for breast cancer, colon cancer, or screening for diabetes

Rochelle Walensky

and directs an AIDS clinic there. A quarter of the people who test positive for HIV infection at his clinic are already in deteriorating health and have fewer than 200 $CD4^+$ T cells/ml blood, which means they have already reached the clinical definition of AIDS and therefore require ARV treatment. These so-called late testers are more often adolescents, an age group where the epidemic is rapidly expanding. "Routine opt-out testing is clearly needed," says Saag, to reach this demographic.

To that end the CDC has revised their guidelines on HIV testing, now recommending that all people between the ages of 13 and 64 should be tested at least once for HIV infection as part of receiving general healthcare, regardless of their perceived risk or the HIV prevalence in that area. Those who are considered at high risk of infection, including men who have sex with men and injection-drug users, should be tested annually, and heterosexual men and women should be retested each time they change their sexual partner or if their partner changes partners.

If these recommendations are adopted—which in most cases would require changing individual state laws that oversee infectious disease testing—the informed consent process specific to HIV testing that was adopted in the 1980s and the VCT approach would be largely eliminated. All individuals visiting a doctor's office, health clinic, or hospital would be informed that they will receive an HIV test unless they expressly decline or opt out. The HIV test would be administered along with other regular tests and a single consent form, signed by the patient, would cover all medical care.

Another reason for introducing a routine testing paradigm now is that testing more people has never been easier or cheaper. The advent of rapid HIV tests, many of which only require a drop of blood or a small sample of saliva, has made it easier for clinics to conduct more HIV tests and results can be provided much more quickly, sometimes in only about 20 minutes. Rochelle Walensky and her colleagues at the Epidemiology and Outcomes Research Group at the Harvard Center for AIDS Research have shown that introducing routine HIV testing is now a cost-effective approach in all areas that have an HIV prevalence greater than 0.1%, which is true throughout the US (*Am. J. Med.* **118**, 292, 2005). "HIV testing is more cost effective than testing for breast cancer, colon cancer, or screening for diabetes, tests that are routinely conducted in the US," she says.

The CDC's goal is to mainstream HIV testing so that it becomes as common as a cholesterol check. Lumping together a test for what was once an untreatable and highly stigmatizing viral infection with the routine battery of medical tests reflects how far AIDS treatment has progressed in

HIV infection eventually declares itself. People need treatment whether or not they're diagnosed

Bernard Branson

wealthy countries over the last 25 years. Although taking ARVs is still difficult because of unpleasant side effects, drug regimens are now much simpler and have, for the fortunate minority who can afford therapy or gain access through treatment programs, turned AIDS into a chronic disease. Public health workers are hopeful that treating the diagnosis of HIV/AIDS like other chronic diseases will help remove some of the stigma associated with the virus.

Others argue that this is an invalid comparison. "This conveys a real misunderstanding about what living with HIV in America is like today," says David Ernesto Munar, associate director for policy and communications at the AIDS Foundation of Chicago. "The emotional and psychological issues are so great. It's nothing like a cholesterol test."

Need for counseling?

In the 1980s AIDS activists demanded that HIV testing be conducted differently because of the pervasive stigma associated with a sexually-transmitted infection that affected mostly white, homosexual men. This brought about several unique initiatives, including the VCT approach that is still in practice today that emphasizes pre- and post-test counseling and HIV-specific education, regardless of whether a person tests positive or negative. But in the CDC's new guidelines, counseling in conjunction with an HIV test "is not required," and this has become one point of contention.

Some argue that without pre-test counseling a person will be ill-prepared for the consequences of an HIV diagnosis and, since post-test counseling will probably only be provided to those who test positive for HIV infection, people who are not already infected would receive little education on how to reduce their risk in the future. Branson says the CDC's goal is to initially target those who stand to benefit the most from HIV counseling. Research studies show the positive effect HIV counseling has on individual risk behaviors and therefore the HIV transmission rates in those who test positive. The CDC itself conducted one study in 1998, known as project RESPECT, which found that consistent use of condoms was more likely in groups that received pre- and post-test counseling and that this group also had a marked decline in the rate of sexually-transmitted diseases. This study, however, didn't look at behavior differences between those who tested positive or negative for HIV infection. "It's very hard to find studies that look at the impact of counseling in people who test negative for HIV," says David Holtgrave, professor in the department of health, behavior, and society at Johns Hopkins University.

If the prevention landscape changes and new options—such as pre-exposure prophylaxis—become available, the CDC will consider changing their recommendations on counseling to also include those who are uninfected, says Branson.

Reactions

Evidence from limited research studies suggests that having more people who know their HIV serostatus will result in fewer new HIV infections. Data indicates that HIV transmission rates among those who are aware of their HIV status are around 2%, compared to 9-11% amongst people who are unaware they are infected. Based on this the idea of routine testing has won praise by many in the public health field as a way to not only connect people to treatment and care services but also to improve HIV prevention efforts. "This certainly isn't happening too soon," says professor Lawrence Gostin, of the Center for Law and the Public's Health at Georgetown University Law Center.

But many civil and human rights advocates are opposed to routine testing. They say it creates a situation where an individual is less likely to decline a test because of the power imbalance between the patient and healthcare provider, making testing involuntary. Groups like the American Civil Liberties Union and Lambda Legal say opt-out testing is in violation of basic human rights and that it is a slippery slope from this to mandatory testing. Gostin admits that there will be some individuals whose informed consent will be compromised with routine testing but argues that policies that benefit the most people must prevail when dealing with such an insidious epidemic. "Personal autonomy can no longer trump overall public health when dealing with this epidemic," says Gostin, who authored an article questioning the conflict between public health and civil liberties (*JAMA* **296**, 2023, 2006).

Branson says that people do opt out of testing and that the CDC will be continually assessing whether or not people feel comfortable refusing an HIV test. There are also several anti-discrimination laws in the US that offer protections, many specifically tailored to HIV-infected individuals.

Treatment access

Ultimately, as in Botswana, the success of the CDC's routine testing initiative will be measured by how many people are linked to treatment and care services. But many question whether clinics and the current funding systems in the US, like the Ryan White Care Act and the AIDS Drug Assistance Programs, are prepared to handle an influx of HIV-infected people. Statistics indicate that the majority of people with HIV are considered low income and are less likely to have private insurance, which might cover the yearly cost of ARV treatment—around US$12,000 to $15,000.

"We have a problem already," says Levi. "We already have a lot of people diagnosed with HIV who aren't receiving care." He estimates that about 250,000 individuals in the US, who are known to be infected, aren't receiving treatment. Adding another quarter of a million HIV-infected people into the system, many of whom may need treatment immediately, would require significantly more capacity and funding. The CDC argues that just identifying HIV-infected individuals isn't in itself adding to the problem. "HIV infection eventually declares itself," says Branson. "People need treatment whether or not they're diagnosed."

Physicians like Saag still maintain that their clinics are already at capacity and that a dramatic increase in federal or state funding would be needed for them to provide the complex treatment and care services to more HIV-infected patients. Yet in 2006 the approved budget for the Ryan White Care Act—federal legislation that provides funding for the medical care of people living with HIV/AIDS—actually decreased. "The idea that the funding pie is fixed is wrong," says Saag. "If you have a growing epidemic, you have to pay for it."

Without more funding researchers worry that the connection between testing and treatment will not be made and so more testing will do little to stem the number of new infections. "We shouldn't be looking for the needles in the haystack if we're only going to throw them back in," says Walensky.

Many of these issues will continue to be discussed and debated in the future. If routine testing is widely adopted critics will be closely monitoring how many HIV-infected individuals end up actually accessing treatment, which they say is the only way to truly measure the success of the initiative and was the key to Botswana's dramatic turnaround.

But it remains to be seen how many states will adopt the new CDC guidelines. In most cases implementing routine testing programs will require altering individual state laws, meaning state officials will have to navigate through murky territory and come up with testing policies that aren't in violation of their existing privacy, consent, and human rights laws. For now, the agency's recommendations remain just that. "Everything that comes out of the CDC is a recommendation," says Branson. "It's not the FDA [US Food and Drug Administration]; we're not a regulatory organization."

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>
> ***Rochelle Walensky***

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This phenomenon, often referred to as brain drain, is attracting increasing international attention, with conferences, declarations, and programs dedicated to stemming the departure of professionals from their posts in resource-poor countries. Most of these efforts have focused on healthcare workers after the massive scale-up of AIDS treatment programs in developing countries laid bare the shortage of qualified clinicians needed to implement them. However, relatively little attention is being paid to what many view as an analogous and related phenomenon of brain drain in the health *research* sector. Available evidence suggests that a significant proportion of biomedical and clinical researchers from developing countries leave their countries of origin or never return after training abroad. The result is a shortage of qualified scientists needed to investigate health problems of national importance, track illnesses, evaluate clinical programs, collaborate with international researchers, improve health systems, inform public policy, and train succeeding generations of researchers and technicians.

In some countries… political leaders are endeavoring to build the research workforce with the understanding that it will contribute to sustained development

Large-scale problem

The US has the largest number of working scientists and engineers of any country, but over a third of those who hold doctorates and well over a quarter of those with masters degrees are foreign-born. According to US census figures from 2000 analyzed by the National Science Foundation (NSF), they hail, in large part, from low- and middle-income countries (National Science Board; *Science and Engineering Indicators 2006*; www.nsf.gov/statistics/seind06/). This trend may well continue. NSF surveys indicated that about three-quarters of all foreign-born doctoral students planned to stay in the US after receiving their science or engineering degree. The situation is similar in other developed countries.

Clearly, brain drain is one of the reasons that developing nations are home to relatively few highly trained researchers. More than two-thirds of the world's researchers live in developed countries. Staggeringly few researchers live in the least developed countries—only 4.5 researchers per million inhabitants. That compares with 374 researchers per million inhabitants in other developing countries and 3272 per million in developed countries (United Nations Educational, Scientific, and Cultural Organization, *Science Report 2005*; www.unesco.org/science/psd/publications/science_report2005.shtml). Often researchers from developing countries have received government support for their higher education and so their departure also represents a loss of investment for their countries.

Weighing the effect

Some social scientists have argued that the migration of researchers from developing to developed countries can have positive implications for their home countries. Well-paid professionals send money home, and they help set research agendas in powerful nations and within development agencies. In fact, experts suggest that the cyclical movement of researchers between countries might actually lead to 'brain gain' for poor countries through the sharing of knowledge. Further, the prospect of enjoying economic opportunities abroad might encourage children in poor countries to obtain higher education.

Some commentators have even questioned the need for qualified researchers to be well-represented across the globe—building research infrastructure requires significant investments, and specialized research programs cannot exist everywhere.

However, a strong domestic research and development capacity in science and technology is tightly linked to economic development. The leaders of highly industrialized nations understand this, and the loss of their own trained researchers concerns them. In recent years the European Union has undertaken several major efforts to plug the brain drain of European biomedical researchers flowing to the US. In some countries, including China, India, and the Gulf States, political leaders are endeavoring to build the research workforce with the understanding that it will contribute to sustained development.

When it comes to developing countries, there are many reasons why indigenous researchers are needed at home. "We're in a better position to know conditions that are very common here and that matter to us and therefore need to be researched," says Mulenga. The capacity to set national research priorities—and devote funds to them—can be critical for developing countries because many of the major medical problems affecting their populations have traditionally escaped the interest of northern research institutions. This problem has been termed the '10/90' gap, reflecting studies in the 1980s and 1990s showing that less than

10% of global health research money was being used to investigate 90% of the world's health problems.

As support grows for AIDS, tuberculosis and malaria programs, the scales may be shifting but they are still far from balanced according to experts at the Council on Health Research for Development (COHRED), a Switzerland-based international organization devoted to building health research capacity in resource-poor countries. Critical underinvestment in health research relevant to problems common in low- and middle-income countries persists. Developing country problems such as malnutrition, childhood disability, and the impact of local environmental degradation on health have received little attention from researchers in industrialized nations, according to COHRED director Carel IJsselmuiden of South Africa. These areas of research will remain neglected, he says, "unless there is some kind of national ability to decide on priorities, conduct research, and find appropriate partners in the north to do it with you."

Sometimes developed and developing country medical research interests coincide, such as with HIV/AIDS and tuberculosis. Here again, the existence of highly trained researchers in developing countries offers distinct advantages. As collaborators they can facilitate the conduct of research in their home countries, settings with a high prevalence of infection and an epidemiological context where new drugs, diagnostics, or vaccines could one day prove most useful. "When it comes to the people you're studying, you're in a better position to know them, know their culture and the ways they understand things," says Mulenga. That helps indigenous researchers ensure that prospective volunteers receive the information they need to provide truly informed consent.

Involving these researchers also increases potential volunteers' trust in the research program, says Pat Fast, director of medical affairs at IAVI. "We want populations and governments to trust that research is conducted appropriately, both from an ethical and a scientific standpoint, so if the research provides a vaccine it will be quickly accepted," she says. "That's best done by having researchers from the country or region conduct the research."

Push and pull

Brain drain occurs due to push factors that drive researchers out of their jobs or native countries, and related pull factors that entice them into other jobs and other nations. Budding scientists often leave their countries to pursue advanced studies and many of them fail to return home. A study released by AfricaRecruit in May 2006 found that nearly half of around 600 African diaspora healthcare professionals listed higher education as the top reason for their migration. The next most common reason was the prospect of professional career advancement, which is often limited in home countries. "There's a major deficiency in career structures," says IJsselmuiden. "Even if you are a good researcher and there is political stability, it's still difficult to move up." Promotion is often based on seniority and factors other than merit. "There's more emphasis on who you are and where you came from," he says.

Career advancement is also hindered by poor working conditions in some developing countries. According to the African Health Researcher Forum (AfHRF), African countries on average spend less than 0.5% of their national health budgets on research, an exceedingly tiny amount given that only 1% of total gross domestic product is allocated to health in the first place (*Lancet* **360**, 1665, 2002). Researchers who trained in the sparkling, high-tech laboratories of North America are not used to the spartan infrastructure they'll face back home. Shortages in supplies and equipment, poor management, and an insufficient number of technicians take a toll on researcher productivity, says Professor Job Bwayo, principal investigator at the Kenya AIDS Vaccine Initiative in Nairobi. "They do very well when they're outside, actively involved in research," he says, "but as soon as they come back they lose that because the environment doesn't encourage their research." Studies have offered evidence supporting Bwayo's assertion. Developing country researchers based outside their countries of origin have a significantly higher rate of scientific publication compared with those based inside.

The low priority that some countries place on research is reflected in a common complaint among scientists—that policymakers tend to ignore or dispute their findings. Recently a team of Ugandan and US scientists as well as two other independent research groups found that male circumcision can dramatically decrease HIV transmission. This exciting finding is being further

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>
> ***Veronica Mulenga***

investigated and its potential implementation intensely discussed. Even so, President Yoweri Museveni of Uganda reportedly was skeptical of the conclusion. "By and large the government doesn't know what [researchers] are doing," says IJsselmuiden. "It doesn't get translated into useful knowledge for policymakers to work with." This, too, contributes to brain drain. "If you do research and don't see action taken, you want to go somewhere else."

Salary differentials also play major a role in brain drain. Researcher salaries are notoriously low in some developing countries. Steven Wayling manages research training grants at the Special Programme for Research and Training in Tropical Diseases (TDR), a scientific collaboration founded in 1975 and co-sponsored by several UN agencies and the World Bank. Wayling says that some physicians accepted into TDR's PhD training programs have declined to participate. "They say, 'I know I can't earn money as a researcher, so I have to stay in clinical practice and support my family.'"

The need to earn a living wage drives some trained scientists to give up research and take other jobs in their countries, sometimes called 'internal brain drain.' The term is controversial because it is often used to describe researchers who jettison government research in favor of positions with international research initiatives or commercial enterprises. "Researchers who would be able to spend time on [research aimed at benefiting local health systems] are drawn out to projects funded by outside donors," says IJsselmuiden, and he views that as a "major international problem." Mulenga says this extends beyond scientists to research technicians. "Here we have quite a number of NGOs from the US who are running a lot of health projects," she says. "These have managed to attract quite a number of skilled technicians from government laboratories into NGOs."

The pull factor of international recruitment is an often-cited factor in clinician brain drain, especially the efforts of European countries and the US to compensate for critical nursing shortages. Recruitment of researchers may not be as targeted, says IJsellmuiden, but "there's lots of open competition going on. There's no inhibitor for attracting good quality African, Asian, or Latin American researchers into your organization." Special visa categories in the US promote the immigration of highly skilled professionals, including biomedical scientists.

Brain gain

While the UK has issued a ban on recruitment of nurses from developing countries, experts caution against analogous bans against researchers from developing countries. "It's OK for someone in America to go to Europe, whereas it's not OK for an African to go to Europe?" asks Wayling. "It's like two standards." Some researchers move to escape war and persecution in their home countries. Whatever the reason for migration, many experts believe it is important for researchers to circulate, share knowledge, and expose themselves to different learning environments throughout their careers.

Numerous studies have found that the majority of expatriate professionals wish to return to their own countries, and an even greater proportion wish to contribute to them in some way (*Science* **310**, 1602, 2006). They often report that they do not know how, and their native countries have failed to reach out to them. "Those scientists should be supported and encouraged to come back and participate in the research of their own countries," says Bwayo. He says scientists working abroad have been steeped in a "culture of research" they can share back home by mentoring and teaching the next generation. A number of programs have been established to help expatriates share their skills in their home countries. These include AfricaRecruit, UNDP's TOKEN project, and 'diaspora networks' of professionals from various countries. The governments of Singapore, China, and some Eastern and Western European countries are promising top salaries to lure their expatriate scientists back home.

Steps to counter brain drain are also being taken much earlier, beginning with the initial education of a scientist. Training programs, which used to involve several years abroad in Europe or the US, are increasingly offered by developing countries such as Brazil, Nigeria, Kenya, Mali, Thailand, Malaysia, and the Philippines. Researchers who do train outside their countries—with support from their governments or international donors—often must agree in advance to return home and work for a certain minimum period. Using this method has allowed countries such as Thailand to build up a globally-com-

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> ***Job Bwayo***

petitive talent pool while investing in research institutions. Some funding agencies, including TDR, carefully select trainees based less on personal ambition and more on potential to contribute to their countries. "Anyone who applies already has to have a permanent job in a research institution," says Wayling. "They have a position to return to and a career path." TDR supports many of the steps on that career path. Trainees can apply for US$40,000 re-entry grants to help them set up research programs back home. Support is made available to strengthen institutions. Ultimately, many of the graduates win competitive research grants from TDR and other funding agencies. The funds allow them to upgrade their equipment, supplies and facilities, and increasingly to train their own scientists and those from other developing countries. Not surprisingly, TDR boasts a near-100% retention rate of the 1500 or so PhDs it has supported over the past several decades.

A few other groups do similar work in Africa, Asia, and Latin America, including the Special Programme of Research, Development and Research Training in Human Reproduction (HRP) of the World Health Organization; the International Clinical Epidemiology Network (INCLEN), initiated by the Rockefeller Foundation; the NIH's Fogarty International Center for Advanced Study in the Health Sciences; and the Field Epidemiology Training Program (promoted by the US Centers for Disease Control and Prevention). Efforts range from training and supporting local scientists to facilitating access to scientific literature, communications, and exchanges, as well as promoting the uptake of research results by governments and the general public. The AfHRF and other developing country institutions are similarly engaged in building capacity, improving the quality of south-south and north-south collaborations, giving developing country researchers a voice in setting and implementing the global health research agenda, and empowering African scientific publishing.

Some developing country scientists say that collaborating with well-funded teams of foreign researchers has made it much easier for them to stay in their countries. KAVI's Bwayo says that international collaboration with IAVI has brought supplies, equipment, reagents, training, presentations at international meetings, and—just as importantly—salary support. "That's the one best thing that's been done," he says. "There's no incentive for us to go anywhere else." Likewise, there's no incentive to do anything else. Government researchers often supplement their meager salaries with more lucrative work in private medical clinics. The additional income from IAVI makes that unnecessary. "That income compares favorably with that of colleagues doing surgery or obstetrics," Bwayo says. "I don't have to moonlight. I don't have to spend time working in evening clinics… I can do research full time."

International collaborations have their share of problems and frustrations for national scientists. In some cases, the internationals run the show from start to finish—from designing the research to analyzing and disseminating the data. "They have their own research agenda, and locals don't participate in deciding what that should be," says Bwayo. "They only use the locals as a front to allow them to conduct research in the country." Some national scientists complain that international researchers tend to collaborate with the same set of "usual suspects," therefore limiting the potential to build capacity in younger generations of scientists.

Looking to the future

Northern and southern researchers have learned from these experiences, and many now recognize that mutual respect and capacity-building toward self-reliance are critical features of successful collaborations. "The most important thing that we all need to help with is to provide a career path for researchers who want to stay in their countries," says Fast. That involves building up both researchers and their institutions. "This is not something one research organization can completely achieve."

IJsselmuiden agrees. He points out that some developing countries maintain dozens of research contracts with a range of funding agencies. Most of these collaborations include a training and capacity development component, but the various efforts are uncoordinated. A more efficient and sustainable approach would be for donors to work together to support research infrastructure, including universities, local research councils, and perhaps regional centers of excellence. "Integrate vertical programming with horizontal system building," he says. "You build up programs that serve more than one research program." That way an epidemiologist trained in the context of an AIDS vaccine trial could

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> ***Pat Fast***

transfer her skills to another research program once the original trial is completed. "More can be done to make sure health research [contributes to] a country's development, not just product development," IJsselmuiden says, and he hopes TDR will play a "brokering role" between donors interested in integrating their work in this fashion. The Commission for Africa Recommendation on Governance and Capacity Building recently called for $500 million a year over 10 years to build Africa's higher education institutions and $3 billion over 10 years to create centers of excellence in science and technology.

There are also steps that international finance institutions can take to counter brain drain, such as removing tight caps on recruitment and salaries. However, most experts are calling for commitment from political leaders, the local private sector, and national research systems themselves to support national researchers. Capacity-building in biomedical and clinical science must be included in national plans, and research institutions must commit to be accountable, transparent, and sensitive to national health priorities. Only with a self-sustaining research enterprise will developing countries be able to guide the research agenda rather than follow the agendas of whoever funds them.

Ultimately, though, the balance of brain drain to brain gain will depend on the individual decisions of researchers themselves. Job Bwayo, like Veronica Mulenga, has decided to focus his efforts at home. "I can make my maximum contribution to this country by working in this country," he says. "I don't ever want to leave." With AIDS taking an ever larger toll on the continent's talent, hopefully an increasing number of researchers will feel the same.

This article was researched and written in December 2006. Tragically, Professor Job Bwayo was murdered in Kenya on February 4, 2007. A full obituary will appear in the next issue of IAVI Report.

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More can be done to make sure health research [contributes to] a country's development, not just product development

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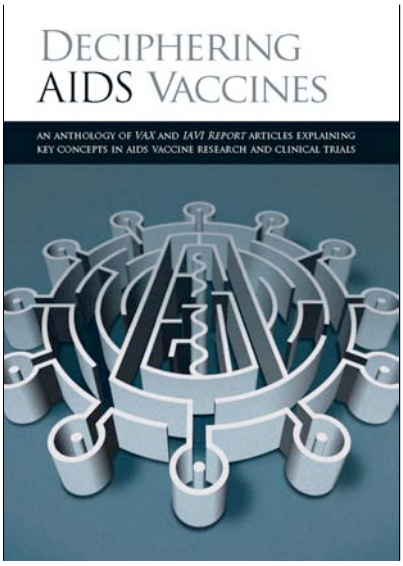
Introducing the new VAX anthology



Deciphering AIDS Vaccines features articles originally published in *VAX* and *IAVI Report*, the only comprehensive publications on the AIDS vaccine field.

This anthology is intended to serve as a general introduction for non-scientists to AIDS vaccines, to educate and inform, to be used by trial sites, volunteers, educators, libraries and anyone else as a vaccine literacy tool.

The articles have been carefully selected to include information regarding all aspects of the AIDS vaccine field and to help the reader understand more about the science of AIDS vaccines and the clinical trials process, as well as alternate HIV prevention strategies and other vaccines that may provide lessons for the AIDS vaccine field. For more information, go to www.iavireport.org.

If you would like to receive one or more copies of the anthology, free of charge, please send your request to iavireport@iavi.org.

Deadly duo: Joining forces to fight TB and HIV

Extensively drug-resistant tuberculosis adds a new dimension to an old public health menace that can act in deadly synergy with HIV

By Catherine Zandonella

When a highly resistant form of tuberculosis emerged in a hospital in South Africa's KwaZulu-Natal province in 2005, its first victims were people living with HIV and AIDS. Within a month of diagnosis, extensively drug-resistant tuberculosis, or XDR-TB, had killed 44 HIV-infected people.

An astonishing one-third of the world's population is infected with the bacterium that causes TB, *Mycobacterium tuberculosis*. Most have a latent form but about 10% of those people will develop active TB disease within their lifetimes. Antibiotics can prevent and treat most of these cases, yet 8-10 million people develop active TB annually and 2 million die from it.

In recent decades the risk posed by TB has been far greater due to the relentless march of the HIV/AIDS pandemic (Figure 1). Stephen Lewis, the United Nations Special Envoy for HIV/AIDS in Africa, has called the two diseases a "combination made in hell." HIV-infected individuals have a 20-fold greater risk of developing active disease, and TB is now the leading cause of death among HIV-infected people around the world.

The global health community is responding by changing how it confronts these two diseases to promote collaboration between historically separate TB and HIV/AIDS programs. A major goal of the World Health Organization (WHO)'s new Stop TB Strategy, launched in 2005, is to decrease the burden of TB and HIV in populations affected by both diseases. The plan is endorsed by a coalition of organizations involved in TB and HIV care, including the Joint United Nations Programme on HIV/AIDS (UNAIDS), public-private partnerships, and non-governmental organizations. "Intensifying collaboration between the TB and HIV control programs in order to ensure the delivery of integrated TB and HIV services in a primary health care platform is crucially needed," says Haileyesus Getahun, secretary of the TB/HIV working group at the WHO.

Around the world the HIV epidemic is making it impossible to continue to confront TB through traditional approaches. The global health community has promoted a program called DOTS since the early 1990s, which stands for directly-observed therapy, short-course. The goal was to bring TB under control through enhanced case detection and short-course antibiotic treatment given under direct observation. This supervision was meant to roll back TB morbidity and mortality while curbing the emergence of drug-resistant strains.

Through DOTS public health officials hoped to achieve a 70% case detection rate and an 85% cure rate by 2005. But while the program has been successful in reducing case rates, according to the WHO, HIV is the main reason for the failure to meet control targets in high HIV prevalence regions. Even when DOTS runs as it should TB rates in HIV-endemic areas continue to rise. In the South African gold mining industry, for example, DOTS adherence is strong and includes yearly TB screens for all miners, and yet the TB case rates have risen four-fold since 1990. During that time, the HIV prevalence has increased from less than 1% to almost 30%.

TB prevention, diagnosis, and treatment services need to be core functions of HIV prevention, treatment, and care services, and vice versa

Haileyesus Getahun

The new STOP TB policy combines DOTS with a greater awareness of the synergy between HIV and TB. Together with the WHO's Department of HIV/AIDS, STOP TB has devised an interim policy that recommends more thorough surveillance and prevention both of HIV among TB patients and of TB in people living with HIV/AIDS. "TB screening for HIV positives or for those attending HIV services is not often done in many settings due to lack of recognition of the importance of TB in people living with HIV," says Getahun. "TB prevention, diagnosis, and treatment services need to be core functions of HIV prevention, treatment, and care services, and vice versa."

Immune consequences

M. tuberculosis and HIV are a deadly combination because both pathogens attack the immune system and induce a complex immunopathology. The precise molecular mechanisms are the focus of much current research. HIV ravages $CD4^+$ T cells and cripples $CD8^+$ T cells. *M. tuberculosis* induces anergy in T lymphocytes, rendering them unresponsive to antigen and effectively paralyzing the immune system. "TB strongly inhibits the immune system to make its

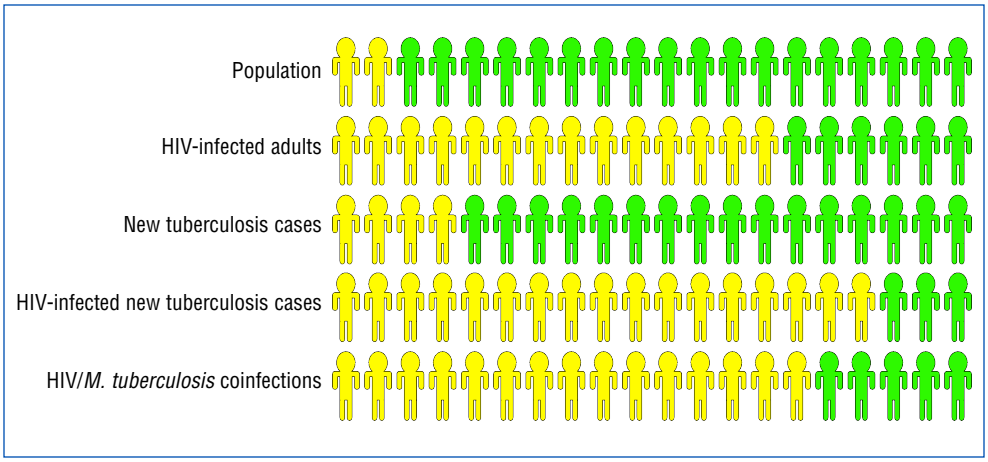


Figure 1. Disproportionate burden of HIV, HIV-related tuberculosis, and *M. tuberculosis* coinfections in Africa, for 2000. *Every person represents 5% of the global total, with African people shown in yellow and the rest of the world in green.* Data taken with authors' permission from *Lancet* **367**, 926, 2006.

Latent infection is far more likely to develop into active TB in individuals with compromised immune systems

way around the body," says Jerald Sadoff, president and chief executive officer of the Aeras Global TB Vaccine Foundation. "Both diseases suppress the immune system independently."

The majority of TB infections are acquired when an individual inhales bacilli shed via the coughing or sneezing of a family member or other person with whom they are in frequent contact. The bacilli lodge deep in the lungs and are kept in check by the immune system, resulting in a latent infection that causes neither discomfort nor infectiousness.

Latent infection is far more likely to develop into active TB in individuals with compromised immune systems. In active TB the bacteria multiply and carve out cavities called tubercles in the lungs. The bacteria can break into the bloodstream and colonize other organs such as the kidneys and brain. Patients with active pulmonary TB develop a persistent cough and can spread the disease to others.

Although TB takes its greatest toll on people with low $CD4^+$ T lymphocyte counts, the disease can affect people at all levels of immune status, making it one of the most common opportunistic infections. While more susceptible to TB, HIV-infected individuals are also less infectious. They are more likely to have extrapulmonary TB so they are less likely to spread the disease through coughing. Also, they quickly progress to advanced TB, giving them fewer years of life in which to transmit the disease.

By contrast, HIV-uninfected individuals may be infectious for several years and able to spread the disease to many immunocompromised individuals. A person with active TB can transmit the pathogen to 10-15 people a year. TB-infectiousness is greatest before diagnosis since most patients become noninfectious soon after starting treatment. This combination of vulnerability to TB among immunocompromised HIV-positive individuals and prolonged transmission from HIV-negative patients with TB is fueling the TB epidemic in areas with high HIV prevalence.

Microbe hunting

Improved diagnostics for TB will be imperative in stepping up surveillance and treatment. The complex interaction between the bacterium and the immune system means that the disease can take a number of forms, some extremely difficult to detect. While HIV can be detected through a relatively simple antibody test, diagnosis of latent or active *M. tuberculosis* infection presents particular challenges. Antibody tests for *M. tuberculosis* have proven useless because the microbe can cross-react with related mycobacteria in the environment. In many regions of the world the techniques used for diagnosing TB have remained relatively unchanged for the past hundred years.

The most common test for latent infection is a skin test where heat-killed *M. tuberculosis* proteins are injected subcutaneously to look for immune hypersensitivity that occurs in people with prior exposure to TB. Though quick and easy, roughly 25% of those with active TB may have negative skin tests, meaning that people who need antibiotics to prevent the transition from latent to active TB will not to get them.

The test does not work in newborns and babies due to their immature immune sys-

tems. Nor does it work well in immunosuppressed individuals, who may be unable to mount the immune response needed for the test to work. "People with HIV often cannot give the immunological reaction that you need to get a positive test," says Hans Rieder of the International Union Against Tuberculosis and Lung Disease in Paris.

The test can also return false positive results, especially in people who've received a vaccination against TB. The vaccine, known as bacille Calmette-Guerin or bCG, is used widely in areas with high *M. tuberculosis* infection rates to immunize infants but its protection is mostly against disseminated infection and lasts only throughout childhood. A new test that measures interferon-γ returns fewer false positives and can be used in areas where people were vaccinated. However, it still returns false negatives and is expensive.

If latent TB is detected then treatment with the antibiotic isoniazid can dramatically reduce the lifetime chance of developing active TB. Yet it is important to make sure that an individual has latent and not active TB since the latter should be treated with an aggressive combination of antibiotics.

Active TB can be diagnosed with a chest X-ray, but it must be confirmed by other methods. The gold standard is the smear test, which involves taking a sample of coughed-up sputum and smearing it onto a microscope slide, fixing and staining it, and then examining for the distinctive cellular appearance of *M. tuberculosis*.

The smear test cannot detect extrapulmonary TB. This smear-negative TB has a worse prognosis than smear-positive disease in people living with HIV. People with HIV often present extrapulmonary cases of TB that manifest as febrile or other disorders that go unrecognized as TB by clinicians.

Growing the sputum sample in culture before searching for bacteria under the microscope can improve the detection of HIV-related TB, but this requires more training and special equipment. "In most resource-poor countries it is a challenge to obtain and maintain a sufficient number of microscopes, let alone more advanced technologies including laboratories for growing and testing cultures or rapid testing technologies," says Rachel Guglielmo, project director of Public Health Watch at the Open Society Institute. Such tests are especially difficult to implement for children, who have a difficult time coughing up sputum.

Keeping TB in check

Preventing the conversion from latent to active TB with isoniazid can reduce morbidity and improve survival. The WHO recommends that all individuals with latent infection, including people living with HIV/AIDS, take isoniazid for six to nine months, but more recent studies indicate that nine months to a year is more effective. In randomized controlled trials, isoniazid reduced the incidence of active TB by about 60% in HIV-infected patients with a positive skin test and 42% overall.

A more recent study sought to determine whether isoniazid could reduce active TB in a community setting. Roughly 700 HIV-infected South African miners were given isoniazid preventive therapy for six months, reducing active TB infection by 38% overall and by 46% in individuals not previously exposed to TB (*JAMA* **293**, 2719, 2005).

A similar effect was seen in a randomized clinical trial involving about 250 HIV-infected South African children (median age 24.7 months). The group receiving isoniazid had a statistically significant lower incidence of TB (5 cases) than did the placebo group (13 cases) (*BMJ* **334**, 136, 2007). The effect was so significant that the placebo arm was stopped and the study may have major public health implications, says Heather Zar, associate professor at the University of Cape Town, who conducted the study. "This could be recommended routinely for HIV-infected children who do not have access to antiretrovirals and who live in high TB-prevalence areas," she says.

But isoniazid preventive therapy is not as widely used as it could be. A study found that only 70% of Swiss physicians put their HIV-infected patients on isoniazid because of concerns over the possibility of a false-positive test, the drug's toxicity, or the development of drug resistance. In developing countries lack of funding and infrastructure compound the problem. Among individuals who comply with the treatment, protection wanes over time, especially in HIV-infected individuals. In areas with high rates of TB transmission, reinfection may be the reason for the failure of preventive therapy.

In addition to isoniazid, the WHO recommends the use of the antibiotic co-trimoxazole as a general preventive therapy for several secondary infections that target HIV-infected adults and children in sub-Saharan Africa. The WHO recommends the drug be given to children up to 18 months old born to HIV-infected

> **[Isoniazid treatment] could be recommended routinely for HIV-infected children who do not have access to antiretrovirals and who live in high TB-prevalence areas**
>
> **Heather Zar**

mothers. Randomized controlled trials have found that co-trimoxazole preventive therapy reduces morbidity and mortality among HIV-infected smear-positive TB patients.

ARVs improve survival

Effective antiretroviral (ARV) therapy can dramatically improve the quality of life and survival time of HIV-infected individuals. The drugs' effective suppression of virus replication allows the immune system to rebound, and several studies have demonstrated that ARVs reduce the incidence of TB in HIV-infected people by greater than 80% (*Int. J. Tuberc. Lung Dis.* **4**, 1026, 2000; *Lancet* **359**, 2059, 2002; *Clin. Infect. Dis.* **34**, 543, 2002). The effect is greatest among people with lower $CD4^+$ T cell counts and those who start ARVs early in the course of their HIV infection. The WHO recommends that ARV therapy be offered to all HIV-positive TB patients if eligible.

A new study presented at the XVI International Conference on AIDS 2006 in Toronto shows that isoniazid plus ARVs may confer the best chance of preventing active TB disease in people co-infected with HIV and *M. tuberculosis*. The analysis of over 11,000 HIV-infected men and women in Rio de Janeiro found that isoniazid plus highly active antiretroviral therapy (HAART) is more effective than either therapy alone at preventing active TB disease—67% disease reduction among people treated with both drugs, while isoniazid or HAART alone reduced disease by 32% and 51% respectively.

The study is one of three ongoing projects by the Consortium to Respond Effectively to the AIDS/TB Epidemic, known as CREATE, led by Richard Chaisson of Johns Hopkins University. Chaisson is also looking at the question of how long HIV-infected individuals should take isoniazid. "We are doing a clinical trial funded by the National Institutes of Health that is looking at giving preventive treatment for an indefinite period of time to see if that is more effective in settings where there is more TB transmission," says Chaisson.

To address TB, some countries may have to revise their guidelines on when to start ARVs. TB occurs at higher $CD4^+$ T cell counts than many other opportunistic diseases, around 250 cells/ml blood, which is higher than the cutoff of 200 where resource-poor countries start to prescribe ART.

Could ARVs exacerbate TB transmission? The possibility exists, since HIV-infected individuals who respond well to ARVs may remain highly susceptible to TB and remain healthier for longer, and therefore able to transmit and acquire TB for longer periods. Reducing this risk, a statistical model found, requires that ARV coverage start early, be comprehensive, and be combined with TB preventive treatment (*AIDS* **17**, 2501, 2003; *Science* **301**, 1535, 2003).

Extensively drug resistant TB

With XDR-TB now present in all regions of the world, global public health officials fear a deadly wave of TB that could spread first among HIV-infected individuals, and then within the general population. About 2% of all TB cases and 10% of multi-drug resistant TB (MDR-TB) cases are XDR-TB, defined by WHO as resistance to at least the two first-line TB drugs (rifampicin and isoniazid) in addition to any fluoroquinolone, and at least one of capreomycin, kanamycin, and amikacin. An estimated US$95 million is needed to stop the spread of XDR-TB, according to the WHO's Stop TB Department.

Identification of MDR-TB and XDR-TB in HIV-infected individuals is even more difficult than a simple TB diagnosis. Drug-resistant strains are usually diagnosed via sputum culture, yet smear-negative pulmonary TB and extrapulmonary TB are more common among HIV-infected individuals. The current tools are incapable of identifying MDR or XDR in a patient with extrapulmonary TB.

The success of programs to fight TB and HIV in a concerted manner rests ultimately on the availability and quality of services. Health officials in countries hit hardest by the HIV epidemic must adopt the WHO recommendations and work on coordination of testing for HIV and TB, counseling, and delivery of ARV and TB preventive therapies. While calling on donors to take a greater interest in funding these activities "it is particularly important to increase awareness about TB among people living with HIV, as a first step," says Guglielmo. A joint HIV-TB approach could range from referrals between services to the integration of HIV/AIDS and TB clinics. As the example of XDR-TB indicates, failure to implement HIV and TB prevention and treatment will only serve to worsen the toll on human lives.

Catherine Zandonella, MPH, is a freelance writer whose work has appeared in Nature *and* New Scientist.

It is particularly important to increase awareness about TB among people living with HIV, as a first step

Rachel Guglielmo

Vaccine Briefs

Two new AIDS vaccine trials initiated in Africa

In December researchers at the Karolinska Institute (KI) in Stockholm, Sweden, the US Military HIV Research Program (USMHRP), and the Muhimbili University College of Health Sciences, Tanzania, began a second vaccine trial to evaluate the safety and immunogenicity of administering immunizations of a DNA candidate and a modified vaccine Ankara (MVA) vaccine candidate in a prime/boost regimen. This Phase I/II trial will enroll 60 volunteers in Dar es Salaam, Tanzania.

The multiclade, seven plasmid DNA vaccine candidate comprised of several *env*, *rev*, *gag*, and RT genes was developed at the Swedish Institute for Infectious Disease Control and is based on HIV strains circulating in Tanzania. The MVA candidate, known as MVA-CMDR, was developed by National Institute of Allergy and Infectious Diseases (NIAID) and is manufactured by the Walter Reed Army Institute of Research (WRAIR). In this trial the candidates are being administered sequentially in a prime/boost regimen; meanwhile KI is also conducting another Phase I trial in Sweden evaluating just the MVA-CMDR candidate in 38 volunteers.

Last year at the annual AIDS Vaccine Meeting in Amsterdam, Eric Sandström of KI presented preliminary results of another placebo-controlled, Phase I trial in Sweden where volunteers received the DNA and MVA candidates in a prime-boost manner. This combination seemed to have promising immunogenicity, with 33 of 36 having positive responses—greater than 55 spot forming cells/million PBMCs—as measured by interferon-γ ELISPOT assay.

More recently the South African AIDS Vaccine Initiative (SAAVI) and the HIV Vaccine Trials Network (HVTN), which is part of the US National Institutes of Health (NIH), initiated a second Phase IIb, test-of-concept trial in collaboration with Merck to evaluate the company's adenovirus-based vaccine candidate (MRKAd5). The trial is being called Phambili, which means 'going forward' in Xhosa, and will recruit 3000 volunteers in four South African provinces, including trial sites in Soweto, Cape Town, Klerksdorp, Medunsa, and Durban.

Another test-of-concept trial, known as the Step study, with the MRKAd5 candidate is currently ongoing at HVTN sites in the US, Canada, Peru, Dominican Republic, Haiti, Puerto Rico, Australia, Brazil, and Jamaica.

South Africa is currently hosting other AIDS vaccine trials as well as other HIV prevention trials, but the Phambili trial is the country's largest AIDS vaccine trial to date. It also marks the first time Merck's leading vaccine candidate is being evaluated in a population where the predominately circulating strain of HIV is not genetically matched with the antigens in the vaccine candidate. The epidemic in South Africa is primarily clade C HIV and the candidate is based on clade B. For more information about these or other ongoing preventive AIDS vaccine trials, visit the *IAVI Report* clinical trials database (www.iavireport.org/trialsdb) and the January 2007 Special Issue of *VAX*, 2006 Year in Review, at www.iavireport.org/Vax/VAXJanuary2007.asp.

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The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996 and operational in 24 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI's financial and in-kind supporters include the Alfred P. Sloan Foundation, the Bill & Melinda Gates Foundation, The John D. Evans Foundation, The New York Community Trust, The Rockefeller Foundation, The Starr Foundation, The William and Flora Hewlett Foundation; the Governments of Canada, Denmark, Ireland, The Netherlands, Norway, Sweden, the United Kingdom, and the United States, the Basque Autonomous Government as well as the European Union; multilateral organizations such as The World Bank; corporate donors including BD (Becton, Dickinson & Co.), Continental Airlines, Google Inc., Merck & Co., Inc. and Pfizer Inc; leading AIDS charities such as Broadway Cares/Equity Fights AIDS and Until There's A Cure Foundation; other private donors such as The Haas Trusts; and many generous individuals from around the world. For more information, see www.iavi.org.

Vaccine Briefs

UNAIDS and WHO release new report on global epidemic

In advance of World AIDS Day, which was observed on December 1, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) released a report detailing updated global and regional estimates of the number of people newly infected with HIV in 2006 (www.unaids.org/en/HIV%5Fdata/epi2006). Twenty-five years after the first cases of AIDS were reported the epidemic is still spreading relentlessly around the globe. In 2006 alone, 4.3 million people were infected with HIV, the majority in sub-Saharan Africa (2.8 million). This brings the total number of people living with HIV/AIDS to approximately 40 million worldwide.

Since 2004 the number of people infected with HIV increased in every region of the world. Last year there were 270,000 individuals newly infected in Eastern Europe and Central Asia and 860,000 in South and Southeast Asia. In many regions these new infections are disproportionately occurring in young people. In the Russian Federation, 80% of HIV-infected individuals are younger than 30 years old. The primary route of transmission in the countries of Eastern Europe and Central Asia is still injection drug use and 67% of HIV infections in 2005 were a result of people injecting drugs with contaminated needles and syringes.

However, in eight African countries where sufficient data was available, HIV prevalence has declined among young people since 2000/2001. This trend is attributed to the success of HIV prevention messages targeting this age group that encourage young people to avoid behaviors that place them at risk of HIV infection. Throughout the world women are also continuing to bear the brunt of the HIV epidemic. In sub-Saharan Africa, 59% of the people living with HIV/AIDS are now women.

Despite promising advancements in the availability of HIV treatment in developing countries, 2.9 million people died from AIDS in 2006—the highest number ever reported for a single year. The vast majority of these deaths (72%) occurred in sub-Saharan Africa where the epidemic is still having the greatest impact, but worldwide AIDS is now the leading cause of death in people between the ages of 15 and 59.

The theme of this year's World AIDS Day was accountability and Kofi Annan, secretary-general of the United Nations, said in a *USA Today* editorial that, "as the number of infections continues unabated, we need to mobilize political will as never before." He called on every prime minister, president, parliamentarian, and politician to strengthen protections for vulnerable groups, including people living with HIV, young people, commercial sex workers, injection drug users, and men who have sex with men. Both UNAIDS and WHO emphasize the need to increase and improve prevention efforts that target people who are at greatest risk of HIV infection.

Mounting data on benefits of male circumcision

Results from two randomized, controlled clinical trials in Africa show that circumcision of male adults reduced their risk of acquiring HIV by approximately 50%. These results were released in December after the Data Safety Monitoring Board (DSMB)—an independent committee of clinical research experts, statisticians, ethicists, and community representatives—reviewed the interim data collected in these trials. Based on the substantial benefit offered by circumcision, male volunteers in the control group will now also be offered the surgical procedure. Researchers will continue to monitor the HIV infection rates among all volunteers and will also study how the procedure affects their risk behaviors.

Both of these trials—which took place in Rakai, Uganda, and in Kisumu, Kenya—were sponsored by NIAID, part of the NIH. The trial data confirmed the results of a previous circumcision study conducted in South Africa, which was the first to show that removal of the foreskin offered some protection against HIV infection (see *Cutting HIV transmission* and *Brazil's model approach*, *IAVI Report* **9**, 3, 2005). Based on the mounting evidence that male circumcision offers protection from HIV infection, organizations like UNAIDS and WHO are currently working on recommendations for the implementation of adult male circumcision in countries where sexual transmission of HIV predominates. According to NIAID, studies in Africa have found that circumcision is an accepted practice, with 50-86% of those surveyed saying they would either have the procedure or want their partner to undergo circumcision if it was known to be safe, affordable, and have minimal side effects.

Another study sponsored by US-based Johns Hopkins University is still ongoing to determine if male circumcision reduces HIV transmission from men to women. However, public health experts agree that any intervention that reduces HIV rates in men by 50% will also result in fewer new HIV infections in women.

Vaccine Briefs *written by Kristen Jill Kresge*