



## Spotlight

### China steps up AIDS response

It is estimated that there are 840,000 people currently living with HIV in China, according to official government statistics. This number, which may be an underestimate due to previously inadequate efforts to provide HIV testing, is not exceptionally high considering the country's 1.3 billion inhabitants account for one fifth of the world's population. But the epidemic's spread has worsened in recent years and the United Nations now warns that China is one of five countries predicted to experience the largest number of new infections over the next five years. The number of HIV-infected Chinese could swell to more than 10 million by 2010.

At that rate Asia could overtake Africa as the continent with the highest number of HIV infections in only 25 years time. Experts familiar with China's AIDS epidemic warn that a narrow window of opportunity now exists for the Chinese government to ensure that a much larger epidemic is averted. "There needs to be resources behind the rhetoric," says William Hsiao, professor of economics at the Harvard School of Public Health. And by most accounts the political commitment necessary to avoid this explosion of HIV infections is finally mobilizing.

"The policy is clearly heading in the right direction, but it will take a long time to fix," says David Ho, Chief Executive Officer of Aaron Diamond AIDS Research Center (ADARC) in New York.

This policy shift is partially the result of new leadership. Since President Hu Jintao succeeded Jiang Zemin, the Chinese government has shown greater concern for the health disparities between the rich and poor. China has experienced great economic growth in recent years. This prosperity has caused an even greater gap in the social and economic status of the country's citizens and furthered the spread of HIV, mainly among the rural poor. The new government is cooperating with health authorities to develop HIV/AIDS prevention and treatment programs in the hardest hit areas.

The lessons Asia learned from the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003 are also fueling China's response to AIDS. Ho refers to SARS as the wake-up call. "It had a profound impact on how China viewed its healthcare infrastructure," he adds.

With the Chinese leadership engaged, treatment and prevention resources are finally reaching China's two most affected communities: blood donors and injection drug users (IDUs). The national government is also investing heavily in AIDS vaccine research and the country's first vaccine trial recently began enrolling volunteers in Guangxi province.

"It's very clear that there is a level of engagement that is new and unexpected," says Sarah Schlesinger, research associate professor at ADARC. "Nobody should underestimate the ability of the Chinese authorities to make a change when they put their mind to it."

Despite the response at the national level, the local governments must also get involved. Provincial governments

play an essential role in providing education and outreach programs, and the response at this level varies greatly. In some provinces active local governments are providing outreach to vulnerable populations, including needle-exchange, drug-treatment, and extensive HIV-testing programs. In other regions there is little coordination between the local governments and the healthcare providers.

Joan Kaufman, of the Schneider Institute for Health Policy at Brandeis University, notes that most local officials still regard the AIDS response as the work of the health sector, which is under-funded and has limited power at the provincial level. "Despite the strengthening of the government's response there remains a real lack of understanding at the local level. For example, there is little attention paid to maintaining confidentiality during HIV testing." Kaufman emphasizes that China must act quickly at all levels of government to check the epidemic's spread.

### A tale of two epidemics

China is a country with two distinct AIDS epidemics. The first began in Henan province in the early to mid 1990's due to flawed blood collection practices. This province in eastern

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### Primer

- Understanding clinical research studies

China is one of the most densely populated in the country. It is estimated that hundreds of thousands, perhaps even millions, of rural Chinese were infected while donating blood. The infections in this population soared for two reasons. Blood collectors often re-used blood collection equipment without sterilization and also re-infused red blood cells from donated blood back into donors to prevent anemia, allowing donors to sell blood more often. These practices were a devastatingly efficient way to spread HIV infection.

A report issued by Human Rights Watch in 2003 urged an investigation into these blood collection practices. Even now not much is known about the disease burden in this community. “China is still restricting scientific and medical access to the community of blood donors,” says Chris Beyrer, director of the Johns Hopkins Center for Public Health and Human Rights.

According to Beyrer, the epidemic among blood donors in Henan province is not expected to reach beyond rural areas. But China’s other HIV epidemic is spreading rapidly. More than half of China’s HIV infections are in IDUs. This epidemic started in the southern provinces of Yunnan and Guangxi, along the border with Myanmar, Laos, and Viet Nam. Myanmar is one of the world’s main producers of heroin and it is easily transported across the border into China. The number of IDUs in the country is still on the rise and drug use is now extending to other provinces.

The epidemic is also affecting other communities, though to a lesser extent. Communities of men who have sex with men and commercial sex workers are not as well studied as blood donors or IDUs. According to Shen Jie, director of China’s National Center for AIDS Prevention and Control, the rate of HIV infection among commercial sex workers is expected to escalate in the coming years as heterosexual transmission becomes a major route for the spread of HIV in the country. Sex workers are considered the “bridge” population because they could further the spread of HIV within the general population.

The HIV epidemic in China is now beginning to move outside the concentrated pockets of infections among blood donors and IDUs.

### Outreach for drug users

“China, until recently, was a very hard place to work with IDUs,” says Beyrer. “Now there is a pragmatic and serious response.” This response includes providing drug users with more education about HIV prevention and the establishment of harm reduction programs that treat drug addiction. These include needle exchange programs where IDUs can exchange used needles for clean ones to reduce the risk of transmitting HIV.

Unfortunately the harm reduction efforts are tremendously variable

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within the provincial governments, according to Beyrer. In some regions the police are not cooperating with the healthcare authorities and are stopping needle exchange programs.

China is also starting to allow drug treatment programs for the first time. Heroin users are treated with the drug methadone as a substitute so they can slowly overcome the withdrawal symptoms associated with addiction. Previous drug rehabilitation programs in China required IDUs to enter camps where they were forced to stop taking drugs without any treatment and were required to do hard labor as a means of detoxification.

There are also some advocacy groups and non-governmental organizations springing up in China to support efforts to treat and prevent HIV infection among drug users. But their role is limited. “The non-governmental organizations in China play a much more circumscribed role than anywhere else in the world,” says

Kaufman, who is also the team leader on vaccine preparedness in China for IAVI.

### Moving ahead with vaccine trials

The national government is also investing in vaccine research and development. Many groups are interested in running vaccine trials in China. The country recently started its first preventive AIDS vaccine trial. The European Union, the HIV Vaccine Trials Network (HVTN), ADARC, and CIPRA (a US National Institutes of Health program in cooperation with China’s Centers for Disease Control) are all looking to start testing vaccine candidates in China over the next few years.

The current trial is taking place in Guangxi province and is a Phase I safety study of a DNA vaccine candidate with a modified vaccinia Ankara (MVA) vector developed at Johns Hopkins University in the US and produced in China. Vaccine trials in China will seek to enroll IDUs because there is such a high incidence in this population. A study by the HIV Prevention Trials Network found an incidence of 8%. This study had good participation and retention of volunteers, even in the absence of drug treatment programs.

ADARC is also preparing to conduct vaccine trials in IDU populations. The vaccine candidate that ADARC is currently studying is based on a strain of HIV isolated from an infected individual from Kunming in Yunnan province. This makes it the ideal place to test the candidate in clinical trials. The candidate is a DNA vaccine followed by an MVA booster vaccination. A workshop on vaccine preparedness was conducted in Kunming earlier this year. “There is a general enthusiasm to organize the ethics committees, community advisory boards, and vaccine education materials,” according to Schlesinger.

Preparations for vaccine trials are an important part of outreach to communities at high-risk for HIV infection because they facilitate the introduction of education and prevention programs. “Vaccine preparedness activities must be paired with other prevention strategies,” says Schlesinger.

## Global News

### India changes law regarding generic medicines

India's parliament recently passed legislation that amends the country's 35-year-old patent law regarding the manufacture of patented medicines by generic companies, in order to allow the country to join the World Trade Organization. Indian companies will now have to pay a licensing fee to the patent holders to continue producing the currently available copied drugs, known as generics. The new law also limits the ability of generic manufacturers to copy patented drugs in the future.

Since Indian companies are a major supplier of discounted antiretroviral (ARV) drugs, many fear that the law could prevent newer and better medicines from reaching the majority of people with HIV. Companies like Cipla and Ranbaxy supply affordable ARVs to millions of people in several countries. This new policy could mean that newer generics, if available, will come with much higher prices.

"It is unclear how these drugs will be made available in the future. It could hamper access to medicines because India has played such a huge role in providing drugs throughout the developing world," says Rachel Cohen, a US advocacy liaison at Doctors Without Borders. Cohen credits the actions of activist groups for influencing the Indian parliament from passing further limitations on the production of generic medicines.

### New reports on Africa ring familiar: More international funding needed

Two recently issued reports on Africa outline probable future scenarios and logical steps for tackling the continent's poverty and the spread of HIV/AIDS. One report issued by UNAIDS (Joint United Nations Programme on HIV/AIDS) proposed three scenarios of how the AIDS epidemic in Africa could unfold over the next twenty years if more funding is not made available for treatment and prevention.

Without \$200 billion in international investment, UNAIDS warned that nearly 90 million Africans—more than 10% of the continent's population—could die from the disease. UNAIDS predicts that 43

million new HIV infections could be averted if the funding is made available, but this amount far exceeds what is already pledged.

Another report was released by The Commission for Africa, an international panel chaired by Prime Minister Tony Blair. This report provided an analysis of the problems that plague the continent and suggestions on how other nations can encourage development in Africa. The commission's recommendations include debt relief, an immediate \$25 billion per year increase in aid, and tackling corruption.

The Prime Minister will push for the G8 countries to endorse the proposals in the report when the group of industrialized nations meets later this year. Blair believes this is a moment of opportunity for Africa. "The lesson of the past few years is that we can't, for our national interests, ignore other countries and continents. So for reasons of self-interest as well as morality, we can no longer turn our back on Africa," Blair commented in a piece from *The Guardian*.

### Merck HPV vaccine candidate effective against multiple strains of the virus

An experimental vaccine has been shown to be effective in preventing infection with four of the most common strains of human papillomavirus (HPV) in 90% of women who were part of a recent clinical trial. HPV is a sexually transmitted disease that causes genital warts and can lead to cervical cancer in women. Cervical cancer is responsible for 250,000 deaths among women each year and is especially deadly in the developing world where women are not regularly screened for this type of cancer.

This vaccine candidate, developed by US-based Merck & Co., is made from a virus-like particle that cannot cause an infection and offers protection against the four strains of the virus that are most likely to cause cancer. Previous candidates from Merck were only effective against a single strain of the virus. In the trial 277 women received three injections with the vaccine candidate, known as Gardasil. These women were compared with a control group of 275 volunteers who received a placebo, or an inactive vaccine. All women in the study were between the ages of 16 and 23. Over the course of the three-year trial, 36 women

in the placebo group experienced an HPV infection compared to only 1 in the vaccine group.

The company plans to approach the US Food and Drug Administration later this year for approval of the vaccine candidate, after collecting results from a larger clinical trial. Gardasil is one of two HPV vaccines in late stage testing. GlaxoSmithKline in the UK and MedImmune in the US are developing the other candidate. This vaccine showed similar results in clinical trials against two strains of HPV.



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IAVI is a scientific organization founded in 1996 whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. IAVI focuses on four key areas: accelerating scientific progress; education and advocacy; ensuring vaccine access and creating a more supportive environment for industrial involvement in HIV vaccine development.



### What information can clinical research studies provide?

AIDS vaccine candidates must go through pre-clinical, Phase I, and Phase II testing before advancing into large-scale Phase III efficacy trials, which test the ability of a vaccine to protect against HIV infection or slow disease progression. But before Phase III trials begin, researchers use clinical research studies to determine the practicality of conducting research in a given community and ready a trial site and community for future vaccine (and other HIV) research trials. Such studies provide critical information about how to design efficacy trials and in which populations it is most appropriate to test vaccine candidates.

Efficacy trials enroll thousands of volunteers who are followed for several years. Running clinical research studies prepares the site for the recruitment and retention of a large number of volunteers. These studies also encourage the development of local scientific research centers, which provide the critical infrastructure for future trials. These centers must be able to meet the technical demands of running large trials, including the capacity to collect data, perform a large volume of laboratory tests, evaluate study procedures like physical exams, as well as to provide general healthcare for the many volunteers.

Clinical research studies also help strengthen the local health care system in order to support future trials. Any volunteers that become HIV infected during clinical research studies through exposure in the community are referred to local clinics for evaluation, care, and treatment. Pregnant women are referred to programs for the prevention of mother-to-child transmission of HIV.

Many groups that are interested in conducting preventive AIDS vaccine trials first conduct clinical research studies. The HIV Prevention Trials Network, the Botswana-Harvard AIDS Institute Partnership, IAVI, and others are engaged in research studies in different communities, many in eastern and southern Africa.

### Prevalence and incidence studies

Determining the prevalence of HIV infection in a community is one important type of research study. Prevalence is the percentage of people infected in a

population at a specific time, calculated based on results from a sample of the population. All volunteers in prevalence studies are provided with comprehensive voluntary counseling and testing (VCT) for HIV.

The process of VCT in clinical research studies includes gathering relevant background information as well as information on sexual practices, condom use, and history of sexually-transmitted disease. This comprehensive VCT process prepares healthcare workers and counselors at each site for the management of large groups of volunteers. Over 20 times more people may need to receive VCT than are actually eligible for a vaccine trial. Many participants may not be willing to participate, while others may not qualify for the study.

Volunteers who are at risk of HIV infection but are not already infected can enroll in HIV incidence studies. HIV incidence is the rate of new infections per year, measured by determining the number of new infections in a specific population over a given period of time. Researchers need to know the incidence in a community to calculate how many volunteers to enroll in an efficacy trial in order to show if a vaccine prevents HIV infection or slows disease progression. Previous research studies have shown that HIV incidence often declines in areas where extensive VCT and public health campaigns promoting HIV education take place.

Incidence studies may include several thousand volunteers per site and last 2-4 years. Participants receive VCT at least every three months. The Botswana-Harvard AIDS Institute Partnership is currently conducting a research study in Botswana in collaboration with the HIV Vaccine Trials Network to evaluate HIV incidence.

### Studying early infection

Another type of research study follows a subset of volunteers from incidence studies that recently became infected with HIV through exposure in the community. This allows researchers to learn the characteristics of the virus strain that establishes an infection and the immune system's early response to HIV infection. Vaccine researchers hope to learn how to design AIDS vaccines from these studies.

Monitoring volunteers that are newly

infected with HIV also provides a general picture of the natural course of infection in the community. Understanding how HIV infection normally progresses will help researchers evaluate if a candidate is effective at slowing disease progression in vaccine trials. Most of the knowledge on HIV infection has come from studying populations in North America, Europe, and Thailand. This is less relevant to African populations where different strains of HIV are present and the general health of the community may vary. IAVI is currently seeking approval to start this type of research study at six sites in Kenya, Uganda, Rwanda, and Zambia.

### Laboratory reference ranges

Clinical research studies can also help scientists understand the existing health of a local population through laboratory results. This type of study includes healthy, HIV-uninfected volunteers. It is important for researchers to understand the community's background health profile so that when a vaccine trial takes place they can correctly differentiate naturally-occurring diseases and not attribute their symptoms to side effects of the vaccine candidate. Much of the existing data on laboratory results were produced from populations in North America and Europe and might not apply to African populations.

To understand the general health of a population, researchers conduct medical histories and physical exams and analyze the results of a number of laboratory tests. Researchers then establish a reference range for HIV-uninfected volunteers for each individual test result. Genetics, nutritional factors, and the presence of diseases common in the community can affect the laboratory results. Once established these reference ranges will help determine if a volunteer can be included in a vaccine trial and can help researchers assess the health of volunteers during the trial.

Other types of research studies are also looking at the levels of pre-existing immunity to different viruses that are being developed as vectors for AIDS vaccine candidates (see the February Primer on Understanding pre-existing immunity). It is important for researchers to know the level of pre-existing immunity to viruses that may be used as vectors since this might limit the immune response to a candidate vaccine.