HIV prevalence estimates: Fact or fiction?

Science and politics often clash. There may be no better example than the issue of HIV in South Africa. Here, where there are more HIV-infected individuals than any other place on Earth, the science of HIV/AIDS and the use of antiretrovirals to treat those already infected have been incredibly controversial political issues.

Politics has always been at the forefront of the HIV/AIDS pandemic elsewhere as well. Even before it had a name, HIV was a political issue. In the days when it first started spreading in the US, rapidly killing those who became infected, the people who would soon be branded AIDS activists implored the US government to openly discuss and actively confront this new disease. As a result there is more legislation in the US devoted to HIV/AIDS than any other disease.

Now some are suggesting that science and politics may be colliding again—this time in the fundamental way scientists measure the scope of the global HIV/AIDS epidemic. Some epidemiologists, whose job it is to track the progress of epidemics, have called into question the accuracy of global HIV prevalence estimates, which represent the total number of people who are thought to be infected with the virus in a region or country at a specific point in time. Prevalence figures are used by governments, public-health agencies, and donor organizations to gauge the severity of the pandemic and this, in turn, drives decisions about how and where money is spent on both HIV prevention and treatment.

In recent years many of the HIV prevalence estimates have been revised based on improved data. In almost all cases the new estimates are lower than previously thought, sometimes dramatically. As a result the total number of people in the world thought to be infected with HIV keeps going down.

A few years ago The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that 42 million people were HIV infected. As of 2006 the number stands just below 40 million. The question about the accuracy of the estimates was pushed to the forefront recently when India, a country UNAIDS had previously estimated to have five million HIV-infected individuals, cut its HIV prevalence numbers by half.

But more accurate prevalence estimates do not mean that the epidemic is under control. “Even if you cut the [HIV prevalence] numbers in sub-Saharan Africa in half, it’s still a huge problem,” says James Chin, a retired epidemiologist and faculty member of the University of California in Berkeley.

Getting better data

HIV prevalence estimates are generated by epidemiologists using HIV infection data from small subsets of the population. This epidemiological data is then combined with national population estimates in mathematical models. These prevalence figures are often reported as a percentage, meaning that in a given country a certain percentage of the population is thought to be HIV infected.

In South Africa the national HIV prevalence among adults between the ages of 15 and 49 is estimated by UNAIDS to be nearly 19%. The number of HIV infections is not evenly distributed within the population—many countries have epidemics that are still mainly contained within certain regions or in groups that are at especially high risk, such as injection drug users or commercial sex workers. In some regions of South Africa or in high-risk populations, the prevalence estimates can be twice as high as the national estimate.

Since its inception in 1995, UNAIDS and the World Health Organization (WHO) have been releasing annual estimates of regional HIV prevalence and biannual estimates of national HIV prevalence that serve as the standard measure of the extent of the pandemic and therefore are given a great deal of international attention.

There are several factors that contribute to declining HIV prevalence, including the increased or improved surveillance of HIV infection in many countries, better population estimates, and more accurate computer models for estimating prevalence. The positive influence of HIV prevention campaigns also plays a role, though it is often difficult to directly pinpoint.

But in most cases recent revisions to the UNAIDS figures have been based on the collection of better data that more accurately represents the burden of HIV infection in individual countries. Many countries are conducting more rigorous surveillance of their HIV epidemics, both

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in the general population and in high-risk groups, either by increasing access to voluntary counseling and testing services or conducting household surveys that are part of the broader demographic and health surveys (DHS). These household, or population-based surveys, allow researchers to track the spread of several diseases in developing countries and monitor trends in the overall health of a population. In DHS surveys, researchers randomly visit a select number of households in a community and collect medical information from the available family members. Recently this survey was altered to include collection of a saliva sample that could later be used to conduct an HIV test.

Previously prevalence estimates were based primarily on data collected from pregnant women who visit antenatal clinics, one of the few settings where there is almost mandatory HIV testing. The original method of projecting prevalence based on data from pregnant women was established in the 1980s by Chin when he was working at the Global Program on AIDS at WHO, long before the job of tracking the pandemic came under the purview of UNAIDS. The idea was the HIV prevalence data collected from sexually active women would be a good surrogate for national prevalence.

But in most cases this data was not representative of HIV infection for the entire population. Most antenatal clinics are located in urban areas, where the HIV prevalence is generally much higher, and the pregnant women who would take advantage of healthcare generally have a higher income, which introduces another bias. Zambia conducted the country's first population-based health study and found that estimates for HIV prevalence based on the number of HIV-infected pregnant women were identical in urban areas, but neglecting rural populations led to a gross overestimation of the overall HIV prevalence in the country. “Data from antenatal clinics helps monitor trends over time,” says Karen Stanecki, a senior advisor at UNAIDS in Switzerland. But as the revisions have shown, it may not be a good way to predict national HIV/AIDS prevalence. “The intent [with data from pregnant women] is to monitor changes, not to predict the actual number of people who are infected,” says Prabhat Jha, professor of epidemiology at the Center for Global Health Research at the University of Toronto.

Watch out for falling estimates

Following pressure from donor organizations to come up with more accurate prevalence estimates, more countries began conducting population-based surveys instead. As a result the estimates of HIV prevalence often dropped, sometimes precipitously. In 2003 after conducting a population-based survey, Kenya reduced its estimated HIV prevalence from 2.3 million HIV-infected individuals to 1.2 million. “That was a huge reduction,” Chin says.

Following that, more than a dozen other countries conducted population-based surveys that led to revisions in the UNAIDS prevalence estimates. In Ethiopia the total number of HIV-infected individuals was cut by half to one million. Cambodia also lowered its national prevalence estimate, from 1.8% of the population to less than 1%. India was one of the latest countries to release new figures showing that the estimated national HIV prevalence is only half of what was previously projected by UNAIDS.

Now 30 countries have conducted population-based surveys to help better estimate the extent of their HIV/AIDS epidemics. In Benin, Mali, and Niger the results from these surveys were nearly identical to the figures estimated using data from antenatal clinics, but in the majority of cases the new figures were lower. Population-based surveys have several advantages—they reach more individuals in rural areas and include men, who are obviously excluded from surveys in antenatal clinics. But they have disadvantages as well. “The other side of the coin is that people may refuse HIV testing,” says Stanecki. “This introduces a bias.” These household surveys are also limited to countries where there is a well-developed HIV/AIDS epidemic. “We don’t recommend that they be conducted in countries with low-level prevalence,” Stanecki adds. Population-based surveys are only applicable in countries where 1% or more of the population is HIV infected, which excludes many countries.

These surveys also tend to exclude marginalized individuals who are often at the highest risk of HIV infection, including injection drug users, commercial sex workers, or transient workers. In countries where the HIV epidemic is still confined within high-risk groups, population-based surveys could therefore drastically underestimate the total number of infected individuals. To adjust for these discrepancies epidemiologists count on other data collected specifically within these populations. But the models are still rather imperfect. “There’s always going to be a lot of bias,” says Seth Berkley, president of IAVI, who was involved in tracking the HIV epidemic in Uganda when epidemiologists first starting estimating prevalence there. But for most diseases there are few people concerned about the accuracy of prevalence estimates. “The numbers for HIV are probably better than for any other disease ever,” adds Berkley. “It’s AIDS that has been the big controversy.”

Also, the onus of collecting better data falls on the individual countries that have to pay for and conduct population-based surveys. “We don’t do any surveys,” says Stanecki. “Surveillance is done by the countries themselves.” UNAIDS and WHO work with countries, holding regional training workshops on the modeling tools and assisting with calculations of national HIV prevalence estimates.

Politics at play

There are obvious political reasons both for and against individual nations collecting better data on the scope of the HIV/AIDS epidemic. Some countries are motivated to conduct household surveys to show that the epidemics are not as bad as estimates suggest and to prove to the international community that the government is handling the epidemic. Other countries may be leery of showing that there is less of an HIV/AIDS problem because it could result in funding cuts for the country’s AIDS-related programs. This controversy was reignited when India’s National AIDS Control Organization (NACO) released new prevalence estimates in July, in cooperation with UNAIDS and WHO.

NACO reported that the new estimates were the result of a considerable increase in the number of HIV testing sites in both rural and urban areas and in low-prevalence Indian states, as well as
Innovation funding announced for AIDS vaccine research

IAVI recently launched a US$10 million initiative to actively identify and fund small- and medium-sized biotechnology companies that are developing innovative technologies in an effort to bring these novel approaches to bear on the research and development of an effective AIDS vaccine. This new funding mechanism, called the Innovation Fund, was announced at the annual meeting of the Clinton Global Initiative, which was held September 26-28 in New York City. "Those [analyses] should be put out there for the entire scientific community to comment, along with the conclusions and projections," he says.

Stanecki says this process is already in place. UNAIDS appoints a reference group, including independent scientists and experts, to review the models and publishes all of the findings from this group, she says. But the exact method that was used to establish the new prevalence figures for India has not yet been released publicly. Jha says that, if anything, the Indian experience should argue for making the prevalence numbers "completely transparent in the future."

Mind the gap

Whether or not the numbers are too high, funding and expanding HIV prevention and treatment programs remains critical—only a minority of HIV-infected individuals in developing countries currently receives life-saving antiretrovirals (ARVs) and last year alone four million people were newly infected with the virus.

There is still an enormous gap between what is needed to control and eventually end the HIV/AIDS pandemic and what is currently being done. "The numbers are lower, but there’s still the possibility of explosive growth," says Jha. There is an overwhelming need for improving the availability of ARVs to HIV-infected individuals in developing countries and new prevention methods, including AIDS vaccines, to help prevent the millions of new HIV infections that still occur each year. "What India, and the rest of the world, should do is focus on prevention especially for high-risk populations and continue accelerating vaccine research," says Jha.
What immediate implications does the cessation of immunizations in the STEP trial have for the AIDS vaccine field?

Merck and the US National Institute of Allergy and Infectious Diseases (NIAID) recently announced that a Phase Ib clinical trial of MRKAd5, an adenovirus serotype 5 (Ad5)-based AIDS vaccine candidate developed by the company, was not effective. The vaccine candidate did not lower HIV infection rates in individuals who received the vaccine compared to those who received an inactive placebo, nor did it successfully reduce the amount of virus in the blood of those who became HIV infected through exposure to the virus, despite vaccination.

The STEP trial—also known as HVTN 502 and Merck V520-023—was co-sponsored by Merck and NIAID, a division of the US National Institutes of Health (NIH). It was the first Phase Ib test-of-concept trial for a candidate that primarily induces cell-mediated immunity, rather than neutralizing antibodies which is how most licensed vaccines work. Phase Ib trials are smaller than traditional Phase III efficacy trials but still allow researchers to collect information about whether or not the vaccine is effective (see VAX September 2005 Primer on Understanding Test-of-Concept Trials).

The STEP trial involved 3000 healthy volunteers at high risk of HIV infection at sites in North and South America, the Caribbean, and Australia. Each volunteer received three shots of either placebo or the vaccine candidate, which uses a virus—in this case one that in its natural form causes the common cold—as a vector to carry three different fragments of HIV. The vaccine candidate cannot cause HIV infection because it only contains some components of HIV. These fragments, known as immunogens, are shuttled into human cells by the viral vector and are then presented to the immune system. This triggers an immune response against HIV that then enables the immune system to recognize and attack HIV in the future.

The STEP trial started enrolling volunteers in December 2004 and was scheduled to end late next year, but immunizations were stopped early when the data safety monitoring board (DSMB), an independent group assigned to review clinical trials while in progress, performed a scheduled analysis of the data in half of the volunteers (see VAX June 2007 Primer on Understanding Data Safety Monitoring Boards). The DSMB concluded that based on the data collected so far, it was unlikely the vaccine would show any effect.

The interim analysis by the DSMB showed that in a subset of volunteers who received one injection of either placebo or the vaccine candidate, there were 24 new HIV infections amongst the 741 volunteers who received the vaccine, compared with 21 infections in the 762 volunteers who received placebo. Another analysis of people who had two injections showed that there were 19 new HIV infections out of the 672 volunteers given the vaccine, and 11 new infections in 691 volunteers given placebo. The differences between the vaccine and placebo groups were not statistically significant, the trial investigators say, which means that the difference in the number of infections was due merely to chance. There was also no significant difference between the amount of virus in the blood of individuals who received vaccine or placebo.

Based on this information, Merck and NIAID decided to discontinue further immunizations. At the time the trial was ended, all but about a dozen of the 3000 volunteers had received all three vaccinations. Another trial testing the same Ad5-based vaccine in South Africa, called the Phambili trial or HVTN 503, was suspended at the same time by that trial’s DSMB. Even though the injections in the STEP study were discontinued researchers are still continuing to follow the trial volunteers in an attempt to gather clues about how the vaccine failed. This information could be incredibly valuable to researchers whose efforts are focused on improving future vaccine candidates.

Other trials

Following the news about the STEP trial, NIAID quickly announced that it would delay the start of its 8500-person Phase Ib test-of-concept trial, known as PAVE 100, which was scheduled to start in October. This trial tests a combination of two different vaccine candidates, a DNA and an Ad5 vector-based candidate, administered sequentially in what is known as a prime-boost combination. Both of these candidates were developed at the Vaccine Research Center (VRC), which is part of NIAID.

IAVI also delayed the start of its Phase II trial, known as V002, in Rwanda, Kenya, Uganda, and Zambia with these same candidates, which was scheduled to begin enrolling volunteers just three days after the announcement from Merck.

Although these trials also involve candidates that use an Ad5 vector, “there are substantial differences,” says Gary Nabel, director of the VRC. He says the VRC’s strategy of using two different candidates in combination induces different types of immune responses. The candidates also contain different HIV immunogens.

The population of volunteers that are involved in the STEP study and the proposed PAVE 100 trial are also different. The STEP study volunteers were primarily men who have sex with men (MSM). In the South Africa Phambili trial, NIAID was testing MRKAd5 in a population where HIV is mainly transmitted through heterosexual sex. In this study over half of the volunteers recruited so far are women, compared to one third of the volunteers in the STEP trial. Researchers think that the route of infection—whether the virus is transmitted vaginally or rectally—may partly determine whether or not the immune responses induced by a vaccine candidate are capable of protecting against HIV infection (see VAX October 2003 Primer on Understanding Routes of Transmission). Like the Phambili study, the PAVE 100 trial will also involve a large number of women who are at risk of HIV infection through heterosexual sex.

New start dates for the PAVE 100 or V002 trials have not been decided yet, but Nabel says he is hopeful PAVE 100 will begin by early next year.