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Spotlight

Moving target

Accurate HIV incidence estimates are critical to the success of prevention trials

The key to winning the classic American game show *The Price is Right* is to come as close as possible to guessing the actual retail cost of a revolving platform piled high with luxury goods, without overbidding. Contestants automatically lose if they overestimate the dollar value. HIV researchers, much like these game-show contestants, are now learning that when it comes to estimating HIV incidence rates—the number of people who are newly infected with the virus over a period of time—there can be serious consequences to guessing too high.

"If you underestimate, that's OK. You just don't want to overestimate," says Zeda Rosenberg, chief executive officer of the International Partnership for Microbicides (IPM), a non-profit microbicide research and advocacy group. Recently two HIV prevention trials of microbicides were stopped prematurely because the observed incidence rate during the trial was so much lower than anticipated that the data safety monitoring board (DSMB; see *VAX* June 2007 *Primer* on *Understanding Data Safety Monitoring Boards*) determined it would be impossible to conclusively show if the intervention was effective or not.

These events, along with trends showing that HIV incidence is declining in many countries, has made many trial sponsors and funding agencies sensitive to the accuracy of HIV incidence estimates. Accurate incidence data are necessary for HIV prevention trials (see *Primer*, this issue). "In order to undertake an AIDS vaccine trial, you need to know the incidence," says Omu Anzala of the Kenyan AIDS Vaccine Initiative (KAVI) in Nairobi.

But accurately determining HIV incidence can be difficult because of the substantial lag time, typically about 10 years, between when a person is first infected and when they develop symptoms of the disease. Consequently many people are unaware of their status until long after they become infected. There are also several logistical challenges to determining incidence rates—many of the quicker methods that have been developed do not work universally and cohort studies where researchers follow a group of uninfected individuals over time, periodically testing them for HIV infection, are expensive and time consuming. Still, most researchers agree that conducting cohort studies to estimate incidence is critical and also offer many peripheral benefits. "The feasibility studies to determine true HIV incidence are extremely important," says Gita Ramjee of the Medical Research Council in South Africa. "They allow you to build capacity so that your Phase III trials are successful."

Global incidence

A handful of countries around the world have aggressively monitored HIV incidence for many years as a way to track their own epidemic's progress. Most often incidence data is reported from antenatal clinics because almost all pregnant women in many countries are tested for HIV infection so that health officials can protect their infants. But this data fails to capture HIV incidence in other groups that are considered at higher risk of HIV infection, including injection drug users (IDUs), men who have sex with men (MSM), and commercial-sex workers.

Thailand, a country lauded for its early and progressive response to HIV/AIDS, began a national surveillance program in 1984 and has been determining annual incidence rates ever since. Early on in the epidemic there was also a national effort in Thailand to determine new cases of HIV infection among particularly high-risk groups. This allowed Thai officials to detect the first wave of the epidemic in these individuals, says Supachai Rerks-Ngarm, a principal investigator at the Thai Ministry of Public Health. "Knowing what the real situation was like was the most important thing we could do to solve the problem," he says. This led to the requirement that all of the country's sex workers use condoms to limit the spread of HIV.

In Uganda, another place where early HIV prevention efforts are credited with stunting an exploding HIV/AIDS epidemic, public health officials started collecting HIV incidence data in 1989. From 1990 until around 2000, the HIV incidence in the general population hovered around 1%, says Anatoli Kamali of the Medical Research Council in Entebbe, Uganda. "This is good, reliable data on incidence," he adds. This low incidence level, compared to other African countries, was attributed to the government's endorsement of the ABC approach (abstinence, be faithful, use condoms). But since 2000 there seems to be a slight

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increase in HIV incidence within the general population, according to Kamali.

In many other countries there is very little current data on HIV incidence. Throughout Asia, for example, reliable HIV incidence data are scarce. Recently India revised its estimates on the number of HIV-infected people in the country based on declines in HIV prevalence among commercial sex workers and within the general population in some of the southern regions of the country (see *Global News*, this issue). Although there is very limited incidence data in India, the Joint United Nations Programme on HIV/AIDS concludes that based on the revised prevalence data, there is probably also a decline in incidence rates.

Even in South Africa, home to the world's largest HIV/AIDS epidemic, incidence data is limited. In 2005 researchers from the Human Sciences Research Council determined incidence rates in 16,000 South Africans and projected that the total number of new infections during the year was 571,000. The highest incidence rate of 5.6% was observed in women between the ages of 20 and 29. But the method used to collect this national incidence data, known as the BED assay, tends to drastically overestimate HIV incidence in African populations (see *Primer*, this issue). Salim Karim, director of the Centre for the AIDS Programme of Research in South Africa, therefore warns that the results from this study should be "regarded as tentative."

Beware of falling incidence

Another complicating factor is that HIV incidence can change rapidly, often declining due to effective prevention campaigns, the recent proliferation of HIV/AIDS treatment programs, and more accurate methods of assessment.

Thailand once had one of the most rapidly expanding epidemics in the world, but now HIV incidence seems to have trailed off outside high-risk groups. When the first AIDS vaccine efficacy trial with the AIDSVAX candidate was conducted in Thailand, the HIV incidence during the trial was 3.4%. In preparation for that Phase III efficacy trial, cohort studies had shown incidence rates as high as 6%. Since the completion of the trial HIV incidence in Thailand has dropped even further.

When the US Centers for Disease Control and Prevention started a Phase III trial in Thailand to test the efficacy of antiretroviral pre-exposure prophylaxis (see *VAX* May 2006 *Spotlight* article, *Treatment as prevention*) for blocking HIV transmission, they enrolled only IDUs because of a higher incidence rate in these individuals. Still this trial is only based on an expected 2% annual incidence.

The ongoing Phase III AIDS vaccine trial, which is evaluating the efficacy of a combination of Sanofi Pasteur's canarypox candidate and AIDSVAX, is also being conducted in Thailand. Rerks-Ngarm reports that among the volunteers at his sites the incidence is low but still within the statistical limits of the study.

The right cohort

Even as the HIV incidence rates drop in many areas, there are still a staggeringly high number of new HIV infections occurring globally—last year alone 4.3 million people were newly infected. Researchers are now considering conducting AIDS vaccine trials in sub-groups of individuals where HIV transmission rates tend to still be very high. "You can go anywhere and if you find the right populations, you can have a high enough incidence," says Karim. But the problem with working exclusively in high-risk populations is first identifying them and then working to recruit and retain them in long-term studies. Many research groups are gaining experience in these areas by conducting prospective incidence studies in high-risk volunteers in preparation for AIDS vaccine efficacy trials.

Kamali and others in several African countries are now working with cohorts of HIV discordant couples, where one partner is HIV infected and the other is not. In Uganda, Kamali's group in cooperation with IAVI has established a cohort of about 500 discordant couples and has observed an incidence rate of around 4%, nearly four times that seen in the general population. Susan Allen, an HIV/AIDS researcher from Emory University in Atlanta, was one of the pioneers of working with discordant couples. At sites affiliated with her program, the Zambia Emory HIV Research Project, the transmission rates among discordant couples ranges between 6% and 9% even with access to counseling and the best-available behavioral interventions.

"We are not just watching people get infected," says Kamali. "We are giving them everything that is available for HIV prevention and even with that comprehensive package we still observe, unfortunately, a high HIV incidence."

Anzala, in collaboration with IAVI, is conducting an HIV incidence study in Kangemi, Kenya involving 701 individuals, including discordant couples and commercial sex workers. Both this cohort and Kamali's discordant couple cohort will be participating in the upcoming Phase IIb AIDS vaccine trial known as PAVE 100. This trial will evaluate the safety and preliminary efficacy of the combination of DNA and adenovirus serotype 5 (Ad5) vaccine candidates developed by the Vaccine Research Center at the National Institutes of Allergy and Infectious Diseases.

Other groups including the US Military HIV Research Program are conducting incidence studies in preparation for AIDS vaccine trials. According to Rosenberg, IPM also plans to conduct incidence studies before starting efficacy trials with microbicide candidates in women at high risk of HIV infection.

In South Africa, where the largest number of HIV-infected individuals live, the HIV prevalence and incidence are generally so high that it is often unnecessary to recruit only high-risk volunteers. "I'm not saying that all the work should be done in South Africa, but you put out the fire where the fire is raging," says Ramjee.

Peripheral benefits

Another advantage of conducting large cohort studies to determine HIV incidence is that they replicate the conditions of a clinical trial, where individuals are receiving regular counseling, education on their risk behaviors and HIV prevention, and have access to condoms. Other methods that have been designed to estimate incidence fail to do this (see *Primer*, this issue). "They look at incidence in populations that are not exposed to behavioral interventions, which could, and likely will, lower HIV incidence," says Matt Price, clinical program manager at IAVI.

Often the HIV incidence will be even lower among volunteers in an HIV prevention study than in the general population. "Every time you start working in a community the incidence drops," says Anzala. "The traditional way [cohort studies] of looking at incidence lets you decide if it is really a suitable community for doing a vaccine trial," says Anzala.

Conducting incidence studies prior to a

clinical trial also provides an opportunity for researchers to cultivate relationships with the community members and leaders, start educational programs that will aid enrollment in future trials, and help establish both the infrastructure and technical know-how among people working at the clinical trial site. The importance of these factors can not be underestimated, according to Ramjee. "There's no point undertaking a clinical trial in an area where you have no community support," she says.

There is also valuable social science research that can be conducted during incidence studies. Researchers can study sexual behaviors and what is putting individuals most at risk for HIV infection, as well as pregnancy rates among female volunteers that can help determine condom use. "Invariably you obtain a lot of scientific data," says Kamali.

Global News

Study shows contraceptive diaphragm does not help prevent HIV infection

The recently completed study of the contraceptive female diaphragm indicates that the cervical barrier does not provide any additional benefit over already available HIV prevention strategies in reducing HIV transmission in women. This first randomized controlled trial of the latex diaphragm was funded by the Bill & Melinda Gates Foundation and was conducted by researchers at the University of California, San Francisco. It involved nearly 5000 volunteers in Durban and Johannesburg, South Africa, and Harare, Zimbabwe. Results of the trial showed that HIV incidence rates (see *Primer*, this issue) among women in the control group who only received condoms and counseling were nearly identical—at around 4%—to those seen in women who also received a diaphragm and lubricating gel. During the 18-month study, 158 new HIV infections occurred in the group of women who received the diaphragm, with 151 occurring in the control group.

Nancy Padian, principal investigator of the trial, says these results do not support adding the diaphragm to the current list of HIV prevention strategies. She promoted the idea of testing the diaphragm, which shields the cervix, as a way to prevent HIV transmission after research showed that the cervix was a potential hot-spot for HIV infection (see *VAX* November 2006 *Spotlight* article, *Capping infection*). Prior to starting the efficacy trial, Padian conducted several acceptability studies to determine if African women were willing to use a diaphragm. As with most HIV prevention methods other than vaccines, compliance is a key factor in determining the success of the intervention. In this study, women who received diaphragms reported using them during only 70% of their sexual acts. These women reported that their partners also used condoms 54% of the time, while women in the control group who were not using the diaphragm reported that their partners used condoms 85% of the time.

Since condom use was lower in the diaphragm group, yet the number of new infections was equivalent, it is possible that the diaphragm contributed to protection. However the trial was not designed to compare the protective effects of the diaphragm to condoms. Researchers are still trying to find ways to help protect women who are at an increasingly high risk of HIV infection and may not be able to get their partner(s) to use condoms.

India revises HIV/AIDS estimates

The National AIDS Control Organization in India recently revised their national HIV prevalence estimates, drastically lowering the estimated number of HIV-infected people in the country to 2.5 million, a figure less than half of that projected by the Joint United Nations Programme on HIV/AIDS (UNAIDS). India was recently thought to have surpassed South Africa in its total number of HIV-infected individuals, based on surveillance data collected from antenatal clinics and high-risk individuals.

The new prevalence data in India reflects the country's efforts to expand their national HIV/AIDS surveillance system. Last year alone the government added 400 new testing sites and also conducted a population-based survey that tested 102,000 individuals for HIV infection. This resulted in a much different estimate of the HIV prevalence within the general population. These new figures are endorsed by both UNAIDS and the World Health Organization.

The additional surveillance shows that in some of the southern states, including Tamil Nadu, the HIV prevalence has started to either stabilize or decline. This is promising news since HIV prevention has been a focus in these regions for several years. But Indian officials warn against assuming the country's HIV epidemic is sharply declining. Surveillance data from 2006 suggests that HIV infection rates among groups at high risk of HIV infection, including injection-drug users and men who have sex with men, are increasing, especially in urban centers.

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Why are HIV incidence rates important for AIDS vaccine trials?

To capture the severity of an epidemic, researchers often refer to prevalence and incidence rates. For HIV, prevalence refers to the number of individuals in a population infected with the virus at a certain time point. HIV prevalence can be determined by conducting widespread testing in a region or country and then projecting the total number of infected people.

Incidence refers to the number of people who are newly infected with HIV over time. These figures are usually reported as a percentage and represent the rate of people who are infected in a year or during another specified period of time. Incidence is more difficult to determine than prevalence, but it is also more valuable because it shows how the epidemic is progressing at the current time. This can help explain the dynamics of the epidemic, the speed at which HIV is spreading in light of current sexual or drug-use behaviors, and the effectiveness of available HIV prevention technologies. Accurate estimates of HIV incidence are also indispensable to the design of HIV prevention trials, including those testing AIDS vaccine candidates.

The "power" of incidence

Researchers are searching for a vaccine that could prevent transmission of HIV. But to test the efficacy of vaccine candidates, some volunteers must become infected through exposure in their community for researchers to know if an intervention is effective or not. Volunteers are never purposely exposed to HIV. Researchers compare the number of infections that naturally occur during the trial between a group of volunteers that received the vaccine and another that didn't.

Statisticians "power" a study to show if an intervention is effective based on the number of people they predict will become HIV-infected during the trial. This prediction is based on the HIV incidence in that population and determines, among other things, how many volunteers must be included in the trial.

If the actual incidence during the course of the trial ends up being much lower than predicted, it can profoundly affect the study. Even small differences can have an enormous impact. In a trial where statisticians assume an HIV incidence rate of 5% and a rate of only 4% is actually observed, 25% more volunteers would have to be recruited or the trial would be inconclusive. Expanding recruitment affects the length and cost of the trial. If the incidence is too low the trial could also be stopped prematurely by the data safety monitoring board (see *VAX* June 2007 *Primer* on *Understanding Data Safety Monitoring Boards*).

For these reasons it is critical to start a trial with the most accurate incidence estimates possible within the specific population where a study will occur.

Ways to measure incidence

The gold standard method for measuring HIV incidence is the prospective cohort study where researchers follow large groups of HIV uninfected individuals over long periods of time, testing them at regular intervals to see if any have become HIV infected, enabling them to determine the rate of infection. These studies are time-consuming, labor-intensive, and expensive, and add substantially to the already complex process of conducting a clinical trial. Consequently some sponsors may use previously-published incidence data to design a study. But this approach can be risky. Two Phase III microbicide trials that were based on previously-published HIV incidence data were recently stopped before investigators could determine the efficacy of the candidates because the incidence during the trials was so much lower than anticipated (see *Spotlight* article, this issue).

There are several other faster ways to estimate HIV incidence. One involves using mathematical models to predict incidence based on existing prevalence data. Another approach is to test large numbers of people for HIV using immunological tests that can identify people who were recently infected with HIV. These tests recognize either parts of HIV or antibodies to the virus that are detectable within a defined period very early in the course of HIV infection. One of the immunological tests or assays detects the plasma levels of p24 antigen, which is an HIV protein that reaches peak levels very soon after a person is infected. Once the immune system generates HIV-specific antibodies, generally within just a couple of months after initial infection, they bind to the p24 antigen and make it undetectable.

Another approach is to use a combination of two HIV antibody tests (ELISA assays) of differing sensitivity. If antibodies to HIV are detectable by the more sensitive test, another test that is purposely made less sensitive is used to see if antibodies are still detectable. The theory is that only individuals who have been HIV infected for a long time would have developed a strong and broad enough immune response to the virus to be detectable by the less sensitive test.

A third method for detecting recent infection is known as the BED assay, because it was originally developed based on the B, E, and D clades of HIV (see *VAX* July 2006 *Primer* on *Understanding HIV Clades*). The premise of this test is that as the immune system ramps up production of HIV-specific antibodies over time, these responses evolve from having a weaker to a stronger attraction or ability to bind to HIV. The BED assay involves an HIV antibody test that measures the percentage of all antibodies that are specific to HIV. This ratio is then compared with a set of predefined parameters to determine if an infection is classified as recent or not.

Unfortunately none of these methods are reliable or work universally—all of them substantially overestimate incidence in African populations and this can be dangerous when starting AIDS vaccine trials. Researchers generally agree that there is no substitute for the traditional cohort study to accurately determine HIV incidence. Several groups, including IAVI and the US Military HIV Research Program, are currently conducting incidence studies in Africa in preparation for efficacy trials of AIDS vaccine candidates.