May 2008 • Vol.6 • No.5

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AIDS VACCINE BULLETIN • WWW.IAVIREPORT.ORG

Spotlight

A static epidemic

Improved estimates still show public health efforts have had little success controlling the number of new HIV infections in the US

Twenty-seven years after the US Centers for Disease Control and Prevention (CDC) published a report detailing a mysterious cluster of pneumonia cases that were later attributed to AIDS, the number of people living with HIV/AIDS in the United States has grown to an estimated 1.2 million, according to the most recent figures (see www.cdc.gov).

The ballooning HIV prevalence in the US can be attributed to the dramatically waning morbidity and mortality associated with HIV/AIDS. Since the days when an AIDS diagnosis was a virtual death sentence, HIV-related deaths in the US have declined significantly—plummeting by more than 70% following the discovery of highly-active antiretroviral therapy (HAART). Once the leading cause of death among Americans between the ages of 24 and 44, HIV is now usually a chronic condition when managed effectively with a combination of antiretrovirals (ARVs) that act on the virus, or its target cells, in different ways.

But what disconcerts public health researchers is the latest surveillance data, which illustrates a static epidemic. In the US, the HIV incidence, or number of new HIV infections that occur per year, has not changed much since 1994. Despite continued efforts to improve education and promote effective and available interventions like condoms, public health agencies have had little success in controlling the number of new HIV infections over the last 15 years.

This worrisome trend will be highlighted in a much-anticipated surveillance report from the CDC that incorporates comprehensive data from state registries and a more accurate method of identifying recently HIV-infected individuals. This new methodology, known as serological testing algorithm for recent HIV seroconversion (STARHS) employs a combination of the normal test or assay for HIV infection, which detects antibodies against the virus, and a less sensitive or "detuned" assay. If antibodies against HIV are detectable by the normal assay, but not by the less sensitive one, researchers using the STARHS methodology conclude that this individual was recently infected with HIV because their antibody responses are not as strong.

The new HIV incidence figures, based on the STARHS method, were submitted to an academic journal last year by the CDC to make sure the methodology, emerging data, and conclusions were scientifically rigorous, and the agency says the data is still undergoing review. The new incidence estimates are widely expected to be announced sometime this year, and they are likely to show that the number of new HIV infections for 2006 was significantly higher—perhaps by as much as 20,000 infections—than the annual estimate of 40,000 new HIV infections per year repeatedly cited by public health departments since 1994. Those familiar with the new methodology say the more accurate epidemiological data probably won't be portrayed by the CDC as a major resurgence in overall incidence, but rather will dramatize how little progress has been made in preventing the spread of HIV among adults, particularly within at-risk populations. "Most likely it is just an upward adjustment and a more accurate estimate of what has been occurring in the last decade," said Walt Senterfitt, a California epidemiologist involved with Community HIV/AIDS Mobilization Project (CHAMP), a national alliance of prevention activists.

The incidence data is also expected to provide a much clearer picture of where the epidemic is heading in the US and eventually offer researchers conducting clinical trials for vaccines, microbicides, and other biomedical interventions more reliable incidence estimates within high-risk populations. This is particularly important for designing future efficacy trials. The Phase IIb STEP trial, which had enrolled 3,000 men and women in North and South America, the Caribbean, and Australia, was stopped in September after Merck's adenovirus serotype 5 (Ad5)-based candidate, MRKAd5, showed no protection against infection (see *A STEP back?, IAVI Report*, Sept.-Dec. 2007). Most of the trial volunteers were men who have sex with men (MSM), but 1,100 were women at high risk of HIV infection. During the trial only one female volunteer in either the vaccine or placebo group became HIV infected.

Researchers said the low HIV incidence in women during the trial was likely due to the lower HIV prevalence among heterosexual men, as compared

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to MSM, in the US. Updated incidence estimates will help researchers identify where women are at a particularly high risk of HIV infection and will inform their recruitment efforts for future HIV prevention trials (see *Primer*, this issue).

Readjusted incidence numbers

The CDC expanded its existing case surveillance system several years ago to include STARHS to try and tease out recent HIV infections from longstanding ones in the population and thereby get a better handle on HIV incidence rates. But this method is not perfect. Three years ago, the Joint United Nations Programme on HIV/AIDS (UNAIDS) said the STARHS method appeared to have overestimated HIV incidence in some African countries and Thailand. But in early studies validating its use in US cohorts the assay performed well, says Harold Jaffe, an epidemiologist formerly with the CDC and now at Oxford University.

Still, Jaffe predicts the new incidence estimates will stir controversy among those who feel AIDS prevention dollars are being squandered, as well as those who believe efforts are underfunded. About 4% of the US$23.3 billion allocated by the government in fiscal year 2008 to fight HIV/AIDS was spent on prevention efforts, according to a Kaiser Family Foundation analysis.

Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), says there is no single reason why the US has hit a "brick wall" in reducing the number of new HIV infections. He says AIDS has lost the terrifying persona that once served as a powerful incentive for careful behavior, while poverty, substance abuse, homophobia, and poor health care continue to put a disproportionate percentage of African Americans at risk for HIV. "This makes it even more compelling for us to find a vaccine for HIV," said Fauci. "It is needed universally and we have reached a point, particularly in the US, where we can't get beyond the 40,000 new infections a year."

Prevention efforts in the US have tended to center around condom promotion and distribution, needle exchange, HIV counseling and testing within high-risk communities, and sex education, including abstinence-only campaigns. Some of these interventions, notably syringe exchange, appear to have helped to reduce transmission of HIV, the latest data shows. But other behavioral interventions launched by state and local health agencies, grass-roots organizations, and faith-based groups over the years have not been well-studied. "When you look at published studies on prevention techniques, they have been done on a small scale. It is difficult to say how well they would work in the general population," says Jaffe. "I think we need to be asking harder questions."

Epidemiologists and social scientists tracking the epidemic tend to think approaches based on behavior change have had minimal, if any, effect in reducing infections within communities shouldering the biggest burden of HIV/AIDS in the US—MSM and African Americans. "I think the reality is that HIV prevention through behavioral change, which is what we have available for adults, isn't that effective," says Jaffe. "Fundamentally, it's hard to change human behavior."

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>
> **Harold Jaffe**

From 2003-2006, the most recent period for which data is available, the estimated number of HIV/AIDS cases increased among MSM but remained stable among adults and adolescents who contracted HIV through high-risk heterosexual contact, according to the 2006 HIV/AIDS Surveillance Report. MSM and persons exposed through high-risk heterosexual contact accounted for 82% of all HIV/AIDS cases diagnosed in 2006, the CDC report says, basing its estimates on data collected from 33 states and five US-dependent areas that have had confidential name-based HIV reporting since at least 2003. Confidential name-based reports include data on patient demographics, HIV risk behaviors, laboratory and clinical events, and virologic and immunologic status. State and local health departments collect the data and forward it to the CDC, minus the patient's name and other personal identifiers.

Women represented 26% of HIV/AIDS cases diagnosed in 2006—compared to just 8% in 1985—and black women accounted for two-thirds of new AIDS cases among all women in 2006, according to the CDC surveillance report.

Though perinatal transmission has declined dramatically in the US since the start of the epidemic, mostly because of the delivery of prompt antiretroviral therapy to pregnant women and their babies, there were still 609 new HIV infections due to mother-to-child transmission between 2002 and 2006, the CDC reported. The agency currently recommends HIV testing of women during prenatal visits and five states even mandate it, but hundreds of infants still slip through the cracks because so many women are becoming newly infected with HIV every year. "We have testing during pregnancy and rapid use of ARVs and other mechanisms. And it still is not eliminated," says James Curran of Emory University.

Infected and undetected

The difficulties of reducing HIV in the US have been underscored by another statistic that public health agencies believe is partly to blame for the static rates of transmission—the CDC estimates about 25% of the 1.2 million people living with HIV/AIDS are unaware that they are infected. Because some of the people with unrecognized HIV infection may transmit the virus unknowingly, perhaps for years because of the virus' long latency period, the CDC expanded its routine testing recommendations in healthcare settings two years ago to include all adolescents and adults ages 13-64, rather than just those considered at high risk of infection. It is unclear as of yet whether this recommendation will help identify these infected individuals, providing them with earlier access to treatment and care services and possibly lowering the chances that they will transmit the virus to others.

Whatever long-term impact the testing guidelines will have in altering the status of the US epidemic, tracking HIV incidence continues to be a complex epidemiological exercise that, paradoxically, seems to grow more difficult as public health agencies become more skilled at collecting and analyzing data. Compounding the confusion has been the mosaic of surveillance systems adopted by different states since the start of the epidemic.

It took 21 years, for instance, for all states and dependent areas to implement HIV case reporting. And it wasn't until 2005 that the CDC recommended that all states and dependent areas adopt confidential name-based HIV infection reporting to better monitor the scope of the epidemic. States are finally on board, but it will be at least three years before the CDC is able to establish trends, particularly at the state level.

Curran said HIV incidence is also hard to determine in the US because compared to AIDS-ravaged areas like sub-Saharan Africa, the incidence in the US is fairly low and the epidemic is not equally distributed across the geographic population.

AIDS advocates frustrated by the failures in curbing the US epidemic want a national AIDS strategy that incorporates more money for prevention, more rigorous studies of existing prevention methods, and better access to health care. "There is a mindset out there now that we will never have behavioral or social strategies that work," said Julie Davids, executive director of CHAMP. "We need to have a combination of approaches that could be rooted in a biomedical intervention." Biomedical interventions could include a preventive vaccine, microbicide, or using antiretrovirals to prevent HIV transmission in uninfected individuals.

With the cost of treating AIDS growing every year in the US, advocates are also increasingly worried about how state and local governments—which shoulder most of the cost—will be able to afford programs over the long haul, elevating the importance of finding comprehensive AIDS prevention strategies that work. —*Regina McEnery*

Global News

World AIDS Vaccine Day commemorated

May 18 marks the 11th annual commemoration of World AIDS Vaccine Day, which is observed to honor the thousands of people working around the world to develop an AIDS vaccine. The significance of this day stems from a Morgan State University commencement address delivered in 1997 by then-US President Bill Clinton in which he called for renewed commitment toward the development of an AIDS vaccine. In the wake of some recent setbacks in the AIDS vaccine field, several organizations consider 2008 to be a particularly important year to raise awareness and support for continued efforts on the part of volunteers, scientists, researchers, and HIV/AIDS advocates to develop an effective vaccine.

This year, organizations around the world coordinated educational campaigns and awareness activities to commemorate the day. The Kenya AIDS Vaccine Initiative (KAVI) hosted an event in Kasarani, outside Nairobi, offering free medical services to local residents as well as free HIV voluntary counseling and testing (VCT) services. The Kenya AIDS NGOs Consortium (KANCO) supported events throughout the country, including a free medical camp based in Kisumu, in the Nyanza Province.

Several organizations in South Africa sought to heighten awareness about the importance of continuing AIDS vaccine research in light of last year's failure of Merck's leading AIDS vaccine candidate, which was also tested in South Africa in a Phase IIb test-of-concept trial, known as Phambili. On May 16, the Desmond Tutu HIV Foundation officially opened its Emavundleni trial site in Cape Town, and community leaders, NGO representatives, and principal investigators participated in the opening ceremony. In Uganda, the Uganda Virus Research Institute (UVRI) and IAVI supported several activities, including setting up a VCT clinic in a fishing community in Entebbe. Alan Bernstein, Director of the Global HIV Vaccine Enterprise, who was visiting Uganda at the time, attended the event.

On May 20, leading HIV/AIDS researchers mark another important day—the 25th anniversary of the study published in the journal *Science* by Luc Montagnier and colleagues at the Institut Pasteur and La Pitié-Salpêtrière Hospital that described HIV as the causative agent of AIDS. A meeting will be held at the Institut Pasteur in Paris in observance of this day at which leading scientists will discuss ongoing research, including sessions focused on current AIDS vaccine efforts. Since the discovery of HIV, over 60 million individuals have been infected with the virus and more than 25 million have died. In an editorial published in the May 9 issue of *Science*, Bernstein said, "The only end for a journey that began 25 years ago should be the development of a safe and effective HIV vaccine." —*Alix Morris, contributing writer*

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VAX is a monthly bulletin from *IAVI Report*, the publication on AIDS vaccine research published by the International AIDS Vaccine Initiative (IAVI). It is currently available in English, French, German, Spanish, and Portuguese as a downloadable pdf file (www.iavireport.org) or an e-mail bulletin.

IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 24 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it. For more information, go to www.iavi.org.

Understanding the Recruitment of Volunteers at Risk of HIV Infection

Why are volunteers who are at high risk of HIV infection necessary participants in late-stage AIDS vaccine trials?

While there are many chapters in the development of a vaccine, its success or failure ultimately rests on its ability to protect the individuals who are at the greatest risk of becoming infected with the pathogen, either virus or bacteria, that the vaccine protects against.

Most routine vaccinations against diseases are now given to infants because they are most susceptible to many viral and bacterial infections. For example, the virus that causes measles primarily infects children, and so the vaccine against measles is administered to infants. This required testing the vaccine in precisely this population. Similarly, for AIDS vaccine trials it is imperative that vaccine candidates are tested in the populations at greatest risk of becoming infected with HIV. This allows researchers to be sure that the vaccine is safe and effective in these individuals.

Phase III efficacy trials of AIDS vaccine candidates require several thousand HIV-uninfected individuals drawn from populations where the HIV incidence—defined as the number of individuals infected with HIV annually—is high. Phase IIb test-of-concept trials, including the recently conducted STEP study, may also involve at-risk volunteers. Phase I and II trials, which are focused primarily on the safety of the vaccine candidate and its ability to induce an immune response, do not traditionally require the involvement of volunteers at increased risk of HIV infection.

Defining high risk

Populations of individuals who are at high risk of HIV infection vary from place to place, and before an efficacy trial can begin, researchers must identify which individuals should be included in a trial. This requires having reliable HIV incidence data in the population in which the trial will be conducted (see *VAX* July 2007 *Primer* on *Understanding HIV Incidence*). When HIV incidence rates are outdated or calculated using old or unreliable methods, it is possible to overlook volunteers who are at risk.

People living in some regions of sub-Saharan Africa, where the HIV prevalence is so high, may be considered at high risk of contracting HIV just by living in a certain place or community. Others are placed at risk of HIV infection by their personal behaviors or occupations, for example injection-drug users (IDUs) who share needles, or commercial sex workers. In the US, men who have sex with men are at the greatest risk of HIV infection (see *Spotlight*, this issue). All of these populations are essential participants in late-stage AIDS vaccine efficacy trials, as their response to candidate vaccines may vary because of the different routes of HIV transmission.

Across the globe, women have been disproportionately affected by HIV. Close to 60% of HIV-infected individuals in South Africa are women, and the number of new HIV infections in women is on the rise in many other countries as well. For this reason it is also imperative that women be equally represented in AIDS vaccine trials (see *VAX* March 2008 *Primer* on *Understanding the Recruitment and Retention of Women in Clinical Trials*). To improve women's participation, trial sites have been encouraged to use counselors and staff who are sensitive to gender, class, and cultural barriers, and to provide transportation and child care for participants.

Risk reduction

While it is necessary for high-risk individuals to participate in AIDS vaccine efficacy trials, their involvement is not taken lightly. Researchers work very hard to ensure that all participants understand what puts them at risk of HIV infection and what they can do to reduce this risk (see *VAX* August 2005 *Primer* on *Understanding Risk-Reduction Counseling*). Risk-reduction counseling is offered to participants throughout the duration of the trial and volunteers are encouraged to be diligent and consistent about protecting themselves against HIV. Despite this, some volunteers will inevitably still become HIV infected through natural exposure to the virus.

Large-scale trials typically measure vaccine efficacy by randomizing study participants into two groups—those who receive a vaccine and those who receive an inactive placebo—and comparing the rate of new HIV infections in each group. For researchers to conclude whether or not a vaccine candidate is effective, some individuals in the placebo group must become HIV infected. But importantly, volunteers are never purposely exposed to HIV.

Other challenges

Aside from providing intensive risk-reduction counseling, there are still several other ethical, scientific, and even geographical challenges that need to be addressed for an AIDS vaccine trial among at-risk individuals to be successful. Often the groups most severely impacted by the AIDS epidemic feel stigmatized and marginalized, and this makes them more difficult to reach. In some places it can be challenging to recruit men who have sex with men, or women, for trials. Most, if not all, study protocols prohibit women from becoming pregnant or breast-feeding during a vaccine trial and this can make it more difficult to recruit women, particularly in cultures where a high value is placed on women's fertility.

Some high-risk communities, such as IDUs, also tend to be more transient, making it difficult to track them through the duration of a multi-year trial. In sub-Saharan Africa, where heterosexual sex is the most common mode of HIV transmission among adults, migratory patterns, low literacy rates, and political unrest are additional impediments to recruiting volunteers at the greatest risk of HIV infection.

The clinical design of efficacy trials is complex, and in response to all of these challenges, counselors and investigators at AIDS vaccine trial sites are continually working to improve their recruitment methods and strategies. Approaches vary depending on where the vaccine site is based and the high-risk population that is being sought. Vaccine sites also rely heavily on community advisory boards and local leaders to assist them in this process (see *VAX* May 2005 *Primer* on *Understanding Community Advisory Boards*).