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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

## Sounding the Alarm

Rates of HIV among black men who have sex with men in the US are skyrocketing, but what's being done?

Thirty-three years ago on June 5, US public health officials issued a brief but haunting report describing an unusual cluster of *Pneumocystis carinii* pneumonia among five, otherwise healthy men, described as “homosexuals” in Los Angeles, CA.

Since then, much has changed regarding the HIV epidemic in the US, but one thing has remained disturbingly the same—men who have sex with men (MSM) still bear the greatest burden of HIV/AIDS in this country, accounting for nearly two-thirds of all new HIV infections in the US in 2010, and nearly three-quarters of the infections that occurred among men, according to the US Centers for Disease Control and Prevention (CDC; *HIV Surveillance Supplement Report 17*, 4, 2011). Moreover, the number of new infections among MSM rose every year from 2008-2010—evidence of a worrisome trend that runs counter to a declining HIV incidence among women and notably black women over the same time period.

While these statistics are disconcerting enough, there is another trend among black MSM in particular that has many researchers alarmed. While white MSM continue to represent the largest proportion of new HIV infections among MSM overall, and incidence is rising among MSM of all races—most rapidly among young MSM aged 13-24—the statistics among black MSM are even more dire. In 2012, black

gay and bisexual men represented almost as many new HIV infections as white gay and bisexual men, despite significant differences in population size. According to the CDC, young, black MSM accounted for 45% of new HIV infections among black MSM overall, and 55% of new HIV infections among young MSM overall.

The catastrophic situation among this demographic has been borne out in many studies. But despite mounting evidence, the notion that epidemics might be different in sub-populations of MSM—and require different interventions—is remarkably still an understudied area, says Phill Wilson, the president and chief executive officer of the Black AIDS Institute in Los Angeles.

“We have an unprecedented catastrophe among young black MSM,” says Wilson. “We need a massive effort to raise attention to the magnitude of the HIV problem among black men. You can’t put out a fire unless you sound the alarm.”

But precisely what that effort should entail and who should deliver it is unclear. Behavioral scientists and epidemiologists are exploring a litany of potential drivers that might explain the disproportionately high incidence among black MSM. Some of the key factors include higher poverty rates, complacency, higher rates of being uninsured or incarcerated, and less access to clinics and doctors who might provide

referrals to care and treatment for other sexually transmitted diseases (STDs) that could increase the likelihood of acquiring HIV. The high prevalence of HIV/AIDS in poorer urban neighborhoods across the US, where mere geography puts one at risk for acquiring HIV, could also be driving a rising incidence, as well as the sexual networks that tend to flourish in these economically disadvantaged enclaves.

Perhaps even more intriguing is what doesn’t seem to be driving higher infection rates among black MSM. An analysis of 600,000 MSM found black MSM are no more likely than other MSM to engage in unprotected sex with HIV-infected partners, yet are more likely to be HIV-infected.

This paradox, researchers found, could partly be explained by the low rates of antiretroviral (ARV) treatment use among the HIV-infected partners of black MSM. Greg

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Millett, a CDC behavioral scientist who conducted this analysis, says HIV-infected black MSM in the US were *less* likely to have health insurance; a high CD4+ T-cell count, which correlates to a healthier immune system; adhere to ARV treatment; or have their virus levels completely controlled by ARV therapy. In other words, even if black MSM were having sex with HIV-infected partners at the same rates as other MSM, the risk of acquiring HIV was greater because the levels of HIV in their infected partners were higher than those in other MSM groups.

Behavioral risk factors also could not explain racial disparities in HIV infection rates found in an earlier analysis, also led by Millett, of 53 studies stretching from 1980-2006 that looked at unprotected anal intercourse (UAI). Black MSM reported less overall substance abuse, fewer sex partners, less gay identity, and less disclosure of same-sex behavior, compared to white MSM, and there were no statistically different differences by race in reports of UAI, commercial sex work, sex with a known HIV-infected partner, or HIV testing history.

Instead, researchers found the high HIV infection rates in black MSM in this analysis were associated with higher rates of other STDs, including gonorrhea and syphilis; less ARV use and more undiagnosed HIV infection; and high rates of UAI early in the epidemic. “Since black MSM tend to have sex with other black partners, greater rates of UAI early in the epidemic may have increased the background prevalence of HIV among black MSM, which has continued to rise to the disproportionately high HIV rates observed today in spite of comparable rates of UAI as white MSM since the 1990s,” the study’s authors suggest.

Other studies have pointed to other factors fueling the spread of HIV among black MSM, including a range of socioeconomic factors associated with poverty and the presence of higher HIV-prevalence sexual networks. Eli Rosenberg, an epidemiology professor at Emory University who led one

of the recent studies of HIV incidence among black MSM, says eliminating these structural determinants—particularly sexual networks and unemployment—would significantly reduce if not eliminate the racial disparities in HIV infection rates. “Structural and community factors seem to be driving this,” says Rosenberg. “How we deal with it is the challenge.”

And given that all these studies point to multiple and different factors that are leading to increased HIV risk, it makes choosing and implementing interventions even more difficult.

### What about PrEP?

While there is an unprecedented amount of data emerging from HIV incidence studies, as well as other studies that offer fresh insights into what is driving the rising incidence among black MSM, none of this research has translated into interventions that seem to be working to halt this alarming spread of HIV. One tool that doesn’t seem to be utilized extensively enough by MSM, and black MSM in particular, is pre-exposure prophylaxis (PrEP), the administration of antiretroviral drugs to HIV-uninfected individuals prior to exposure to reduce the risk of infection.

Nearly two years ago, the US Food and Drug Administration granted the California-based pharmaceutical company Gilead Sciences a license to market the once-daily, two-ARV (tenofovir/emtricitabine) combo Truvada to high-risk HIV-uninfected adults after the drug was shown to reduce HIV infection among MSM by 42%. The CDC has been recommending PrEP for MSM since 2011.

Yet PrEP use outside the context of research studies is sparse, according to a survey conducted by Gilead that used nationally representative anonymous patient data from over half the retail pharmacies in the US. The survey found 1,774 men and women had been prescribed PrEP between January 2011 and March 2013.

Gilead wasn’t able to break down PrEP use by race or transmission risk, but the drug maker did find that nearly half the PrEP prescriptions were for women, a group that accounts for only 20% of new infections. They also found PrEP use was less common in the young. Only 13% of those taking PrEP were under age 24.

“We think the numbers are artificially low, though,” says Gilead’s director of HIV medical affairs Keith Rawlings. “Don’t forget that thousands of MSM are already receiving PrEP through demonstration projects and as they roll off the studies many may continue [with PrEP],” Rawlings contends. There are over a dozen demonstration projects, pilot studies, and rollout studies looking at ways to make the delivery of PrEP feasible within MSM communities.

But preliminary data from one of the earliest demonstration projects, known as The Demo Project, only managed to enroll a handful of black MSM at its study sites in San Francisco, Miami, and Washington, D.C. Most of the 600 HIV-uninfected MSM and transgender women being offered a daily pill to protect them against HIV are white. Enrollment figures reported at the 21st Conference on Retroviruses and Opportunistic Infections (CROI), held earlier this year in Boston, showed 48% of enrollees were white, 35% were Latino, and only 8% were black.

These numbers are a stark contrast to the goal laid out in the Black AIDS Institute’s five-year action plan, which calls for a major initiative to deliver PrEP to black MSM and high-risk heterosexual women by 2015. Wilson acknowledges the goal is ambitious, but he also thinks it’s achievable. “This is a matter of investment and resources,” he says. “We have the tools in our hands. I think the problem is money and political will.”

### A federal response

The passage of the Affordable Care Act in March 2010, which extended health coverage to millions of uninsured Americans,

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and implementation of the US's first National HIV/AIDS Strategy four months later, may also provide opportunities for expanding prevention and treatment services for people at risk of HIV, policy makers say.

The White House also recently appointed Douglas Brooks, a gay, black man living with HIV, to lead the Office of National AIDS Policy, the third person to hold this position in the past six years. Brooks, who grew up in Georgia and lives in Boston, has deep roots in AIDS advocacy. "Douglas's policy expertise combined with his extensive experience working in the community makes him uniquely suited to the task of helping to achieve the goal of an AIDS-free generation, which is within

our reach," remarked US President Barack Obama when he made the appointment on March 25.

### Benefits of testing

More widespread HIV testing is another strategy that would help get prevention messages out to black MSM. According to a CDC analysis, this is one area where a positive trend is occurring. In a study of 16,069 MSM, HIV testing rates rose from 2008 to 2011, with an even greater increase among black MSM. The authors of the CDC analysis, who presented their data at CROI in March, say increasing the number of MSM who are tested and linked to care will improve health outcomes and may reduce HIV transmission.

CDC behavioral scientist Patrick Sullivan, who wrote a special report about the HIV epidemic among MSM in *The Lancet*, says no single HIV prevention approach will be enough to curtail HIV incidence among MSM. But a combination of structural, biomedical, and behavioral interventions that are evidence-based might avert a quarter of new infections in certain countries.

David Purcell, the deputy director for behavioral and social science in CDC's Division of HIV/AIDS Prevention, agrees and says the fight requires action on every level. "Action is needed not only from government agencies, but also from community organizations, and among gay and bisexual men themselves, to ensure all men know their HIV status and take appropriate steps to stop HIV." ■

## GLOBAL NEWS

### PEPFAR's New Leader Faces Challenges as Program Enters Second Decade

The US President's Emergency Plan for AIDS Relief (PEPFAR), which has provided life-saving antiretroviral therapy (ART) to more than 6.7 million HIV-infected people in developing countries since its launch in 2003, is beginning its second decade with a new leader and shifting strategies.

In April, the Obama administration appointed Deborah Birx, a US Army colonel and physician with deep roots in the global AIDS fight, as the new Ambassador at Large and US Global AIDS coordinator, placing her in charge of all international HIV/AIDS efforts, including PEPFAR, making her the program's fourth leader.

Prior to joining PEPFAR, Birx led the US Military HIV Research Program (MHRP) during the launch of the RV144 AIDS vaccine trial in Thailand, which drew intense criticism at the time but eventually made history as the first and thus far only vaccine trial to demonstrate efficacy (see *VAX Sep. 2009 Spotlight* article, *First Evidence of Efficacy from Large-Scale HIV Vaccine Trial*). Birx left MHRP in the midst of the trial to head the US Centers for Disease Control and Prevention's (CDC) global AIDS program.

Nelson Michael, who worked for Birx during the early days of the RV144 trial and took over the directorship of MHRP when she left, said the US\$105 million trial would probably have derailed were it not for her single-minded determination. "It was a rocky time, and there was obviously a lot of discussion in the scientific press," recalls Michael, referring to a policy forum in *Science* magazine in which leading scientists raised questions about the scientific rationale for the large trial. "But if she thinks something is right, nothing will deter her."

One challenge facing PEPFAR, and now Birx, is the process of shifting responsibility of PEPFAR-established programs to the host country's government. PEPFAR, which has already committed more than \$52 billion to fight HIV/AIDS, malaria, and tuberculosis, is now trying to strengthen capacity in recipient

countries so they can manage their own treatment and prevention programs (see *VAX Dec. 2009 Spotlight* article, *A Year of Progress*). Eric Goosby, the previous head of PEPFAR, began this process before leaving PEPFAR late last year to lead a new center at the University of California in San Francisco.

This process of shifting control over to the recipient countries and getting them to shoulder the costs may be more difficult given the increasing political tension over new anti-homosexuality laws passed in several countries, notably in Uganda, the largest recipient of PEPFAR funding. In her first official comment, released a day after her swearing-in ceremony on April 10, Birx responded to this situation. "No matter how challenging the conditions, PEPFAR has never been deterred from continuing to do all we can to support comprehensive, non-discriminatory HIV services for all individuals, and we will not back down now," she said. "As public health practitioners, our core ethical responsibility is to the people whom we serve, and this holds true even when we may disagree with host government policies that are at odds with sound science or good public health."

Along with the anti-homosexuality bill signed into law earlier this year, the Uganda Legislature passed a bill on May 13 that includes mandatory HIV testing for pregnant women and their partners, and allows medical providers to disclose a patient's HIV infection status to others. The bill, which Uganda President Yoweri Museveni is yet to sign into law, also criminalizes HIV transmission, attempted transmission, and behavior that might result in transmission by those who know their HIV status.

Birx responded quickly to the most recent legislation passed in Uganda. "I join with the many health practitioners, HIV/AIDS and human rights activists, multilateral institutions, and individuals everywhere—in Uganda and around the world—in calling for the people and the Government of Uganda to reject this regressive bill," she noted, in a May 14 release. ■

# Understanding the Bulk Production of Broadly Neutralizing Antibodies

How will researchers manufacture broadly neutralizing antibodies for HIV prevention and treatment studies? *By Michael Dumiak*

The isolation of a new crop of antibodies that can inactivate a wide variety of HIV strains remains one of the most important recent discoveries in HIV vaccine research. Antibodies are proteins made by the immune system in response to pathogens such as viruses. So-called broadly neutralizing antibodies (bNAbs), dozens of which have now been isolated, can inactivate a much broader range of HIV strains than any of the HIV-specific antibodies isolated before. Ideally, vaccine researchers will identify an immunogen or set of immunogens—the vaccine components that induce an immune response—which can spark production of these bNAbs in uninfected people.

Meanwhile researchers are using these antibodies in other ways, including what is referred to as passive administration or passive immunization studies (see VAX May 2010

*Primer on Understanding if Broadly Neutralizing Antibodies are the Answer*). In passive immunization studies, researchers directly inject one or more of the recently isolated bNAbs into uninfected people to see if they are able to protect against natural exposure to HIV.

Preliminary safety studies of the passive immunization approach are already underway with one of the recently identified antibodies, known as VRC01, which was discovered by researchers at the National Institute of Allergy and Infectious Diseases (NIAID). Two trials with VRC01 are ongoing in groups of 15 to 25 people—one is a group of healthy volunteers and the other is a group of HIV-infected volunteers. Results from the safety trials are expected in as little as three months, and scientists are already discussing what the next steps could be.

Based on recent non-human primate

studies, there is also the potential for using these bNAbs for HIV treatment or even research toward an HIV cure (see VAX March 2014 *Primer on Understanding the Expanding Role for Broadly Neutralizing Antibodies*).

Taken together, all of these approaches prompt a more basic question: how will researchers produce these antibodies in bulk?

## Machinery for manufacture

Isolating bNAbs is a painstaking procedure, involving finding an HIV-infected volunteer, extracting their immune cells, isolating the genetic material from those cells, screening the genetic material to isolate the code for the antibody, cloning that code in cells, and then finally screening and testing those cells until the antibody can be isolated. This is complex and difficult work that is done on a small scale. While it is sufficient for use in lab research to try to understand the antibody, each procedure generally only produces a maximum of 30 micrograms of protein.

By comparison, the ongoing clinical trial testing VRC01 in humans involves doses ranging from one milligram of antibody per kilo to 40 milligrams per kilo. If an average person weighs 80 kilos, the necessary dose of antibody could be as much as 80 milligrams, or 80,000 micrograms. To manufacture this quantity of antibody for research studies in humans, a more industrial process is required. Making this process more efficient and cost effective could become a pressing issue should these bNAbs be used in the future as part of a treatment or cure strategy.

A dozen or so companies can manage protein production on an industrial scale in what are called bioreactors. Contemporary bioreactors are specialized stainless steel tanks used to cultivate cell banks. These are groups of cloned cells into which scientists have inserted the genetic material of the bNAb in order to multiply. This cultivation is a grueling process which can take months; workers need to find the right temperature and medium in

which to grow the cell bank, and then the antibody needs to be purified from the solution in the bioreactor and tested rigorously. If it is to be made for clinical use, this needs to be done under very strict lab conditions, all of which must be thoroughly documented.

While biotech companies have made advances in purification and bioreactor design in recent years, the basic procedures remain fairly constant. NIAID has its own pilot plant with a bioreactor capable of producing enough VRC01 antibody doses for a Phase I trial. A typical pilot plant bioreactor size runs from 100 to 500 liter capacities, which can deliver five or six kilos of protein per batch. A manufacturing company is likely to use bioreactors that can handle 1,000 to 20,000 liter capacities.

But even given all the technological or feasibility issues, the greatest challenge in scaling up antibody manufacturing is likely to be the cost. Market rates for bulk bNAb protein production could run from US\$30-\$50 per gram, by some estimates. For use on a broad scale, either a developer would need to take on that cost or drive it down to \$3-\$4 per gram, which will be difficult to achieve. The vast quantities of purification solution and the filtering needed to effectively purify the antibody in the bioreactor keep costs high. Manufacturing antibodies is a very sophisticated and challenging operation.

To cut costs researchers are searching for cheaper media in which to cultivate cell lines and purify and extract the antibody solution, and are also considering using smaller single-use or even disposable bioreactors with faster production times. Researchers are also looking for new modes of production. Some scientists think using corn or tobacco plant cells is another way to quickly and inexpensively grow antibodies in bulk. But for now, the cost challenge for production remains daunting. ■

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