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Using ARVs to Prevent HIV Could Result in Drug Resistance if Routine Screening is Not Done New Research Presented at International Microbicides Conference

PITTSBURGH, May 23 – Their scientific methods may have been quite different, but their conclusions were not. In asking whether drug resistance could be a problem if antiretroviral (ARV) drugs become a mainstay for HIV prevention, the two studies – one involving a mathematical model and the other assays of cells and tissue – arrived at the same answer. Resistance could happen if people who are unknowingly already infected use the approach.

The results of these studies, which were reported today at the International Microbicides Conference in Pittsburgh, underscore the importance of incorporating routine HIV testing and ongoing monitoring of infection status in any prevention program that involves the use of ARVs.

Pre-exposure prophylaxis (PrEP), as the approach is called, involves the use of ARVs by HIV-negative people in order to reduce their risk of infection. Several clinical trials are testing whether PrEP can prevent HIV in different high-risk populations. With PrEP, a single ARV is used, typically once a day. While one ARV has the potential to prevent HIV in someone who is uninfected, one drug alone is not enough to suppress virus in someone who is infected, which is why at least three different ARVs, used in combination, are required in the treatment of HIV. If a person who is infected continues taking a single drug, the concern is that virus would become resistant to that drug or drugs in the same class, thereby limiting treatment options in the future.

The current research does not diminish the promise of PrEP and other ARV-based prevention approaches, the researchers say. What the studies provide is a more clear view of what is likely to be needed to ensure that PrEP can offer the most benefit to as many people as possible and with the least amount of risk. It is likely that any successful HIV prevention program which includes the use of ARVs will require routine screening for HIV in order to prevent HIV-infected people from inadvertently using PrEP when they are already infected.

M2010 is taking place May 22-25 at Pittsburgh's David L. Lawrence Convention Center. Nearly 1,000 participants from 47 different countries are attending the meeting to hear about the latest developments in HIV prevention research. Summaries of the two resistance-related studies are provided below.

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Mathematical model identifies key factors that would influence spread of HIV drug resistance if ARVs are used for prevention

Pre-exposure prophylaxis (PrEP) is a promising HIV prevention approach that involves use of antiretroviral (ARV) drugs by HIV-uninfected individuals to protect against infection. But, should clinical trials find the strategy successful and PrEP is then rolled out as a prevention approach in at-risk communities, there is concern that virus resistant to the ARVs potentially would emerge and spread. Indeed, a mathematical model found that if people who are already HIV-infected inadvertently use PrEP, drug resistance is very likely to occur. The finding underscores the importance of routine HIV testing and ongoing monitoring of infection status being a part of any PrEP program, says Ume Abbas, M.D., of the Cleveland Clinic Foundation, who led the study.

Dr. Abbas and colleagues developed a model to simulate the impact of PrEP on HIV prevention and drug resistance in a region of sub-Saharan Africa, where HIV rates are among the highest, and to identify the determinants contributing most to HIV drug resistance prevalence. The model singled out two factors having the most influence, finding that the greater number of people who use PrEP who shouldn't be and the longer they keep using the ARVs, the more prevalent drug resistance would be.

The model looked at different scenarios, including ones representative of the most pessimistic and the most optimistic situations. The optimistic scenario assumed that PrEP reduced the risk of infection by 75 percent, that 60 percent of the at-risk population used it, and 5 percent of the population of individuals who are already infected inadvertently used it. Under these conditions, the model predicted the prevalence of resistance after 10 years to be only 2.5 percent of the population. Under the pessimistic scenario, which assumed a 25 percent reduction in HIV risk with PrEP, 15 percent of the at-risk population being covered and 25 percent of those already infected using PrEP, resistance was expected to affect 40 percent of the population in 10 years. The model took into account age, gender, sexual activity, HIV status, stages of disease and PrEP use and discontinuation and HIV drug susceptibility.

Laboratory studies find ARV-based gels protect against infection with resistant virus

Researchers testing whether antiretroviral (ARV)- based candidate microbicides are effective against strains of HIV known to be resistant to these ARVs and/or drugs in the same class found they were indeed protective in laboratory studies. And in other tests trying to determine whether use of ARV-based microbicides could contribute to the emergence of drug resistant virus, they determined the possibility could exist if HIV infection was already present. Granted, experiments conducted in a laboratory cannot with any certainty predict what will be true in real-life settings, but the results are encouraging nonetheless, says Susan M. Schader, a doctoral student at McGill University and the McGill AIDS Centre in Montreal, Canada. Four ARV-based candidate microbicides were studied, including tenofovir and dapivirine, which belong to a class of ARVs called reverse transcriptase inhibitors that act on a key enzyme HIV needs for replicating itself. Tenofovir gel has already been tested in one clinical trial and another large clinical trial is underway, while a phase III trial of dapivirine is being planned. The researchers also looked at DS001 and DS003, which are in earlier phases of development as potential microbicides for preventing sexual transmission of HIV. Both are entry inhibitors that prevent HIV from getting inside cells by targeting specific docking stations on the cell surface.

There are at least nine known genetic subtypes of HIV-1. In the United States and Canada, most HIV infections are with the B subtype strain, while elsewhere in the world all other subtypes are predominant. Resistant virus is categorized accordingly. As the availability and use of ARVs increases in places like Africa, drug resistance will increasingly be more common. And people who develop resistance could feasibly infect others with virus that is drug-resistant. So, the researchers looked at how well each of the ARVs worked alone and in different combinations against cell cultures containing B subtype drug-resistant virus and three strains of non-B subtype resistant virus. They found each of the four candidate microbicide ARVs potent against the drug-resistant strains, although the ARV combinations (dapivirine plus tenofovir and dapivirine plus DS003) were more effective than any one drug. Interestingly, dapivirine and tenofovir used together was more effective against HIV resistant to

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dapivirine when compared to each drug used alone and to wild type HIV. To evaluate whether the ARV-based microbicide compounds could cause virus to become drug resistant, the researchers infected blood cells with different subtypes of HIV and exposed the infected cells to dapivirine alone and to dapivirine plus tenofovir continuously for more than 25 weeks to induce drug resistance. Drug resistance emerged only if HIV infection was present before the candidate microbicide ARVs were introduced and continued to be used.

More than 33 million people are living with HIV, more than two thirds of them in sub-Saharan Africa, according to UNAIDS. The number of new infections continues to outstrip advances in treatment: For every two people who begin treatment, five are newly infected. Globally, women account for half of all HIV infections, and in sub-Saharan Africa, women comprise 60 percent of all infected adults. Young women are especially vulnerable. In southern Africa women aged 15 to 24 are at least three times more likely than their male peers to be infected with HIV. Meanwhile, men who have sex with men (MSM) bear the burden of the epidemic in the United States and in other parts of the world, such as Europe, Latin America, Australia and New Zealand. According to the U.S. Centers for Disease Control and Prevention, MSM of all races is the only risk group in the United States in which new HIV infections are increasing. Black heterosexual women represent the third highest risk group in the United States, after white MSM and black MSM, respectively.

M2010 is the sixth biennial meeting of the International Microbicides Conference and marks the first meeting in the United States since the 2000 inaugural gathering in Washington, D.C. Other previous meetings have been in Antwerp, Belgium; London, England; Cape Town, South Africa; and New Delhi, India. Co-chairs of this year's conference are Sharon Hillier, Ph.D., and Ian McGowan, M.D., Ph.D., both of the University of Pittsburgh; and Gita Ramjee, Ph.D., of the Medical Research Council of South Africa. The scientific program and other information about the meeting can be found at www.microbicides2010.org.

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