Next front in worldwide AIDS battle: Stretching use of anti-HIV drugs

July 6 2012

(Medical Xpress) -- A Johns Hopkins expert in the drug treatment of HIV disease and AIDS is spearheading an international effort to radically shift the manufacturing and prescribing of combination therapies widely credited in the last decade for keeping the disease in check for 8 million of the 34 million infected people worldwide.

“We can do more with less of the active pharmaceutical agent in many anti-HIV drug compounds and we can adopt more efficient techniques to make the drugs more quickly and for less money than before,” says clinical pharmacologist and infectious disease expert, Charles Flexner, M.D., a professor at the Johns Hopkins University School of Medicine and the university’s Bloomberg School of Public Health.

In a report appearing in the July edition of the medical journal *The Lancet Infectious Diseases*, Flexner, along with other scientists from Johns Hopkins and the Clinton Health Access Initiative, say more efficient and cheaper manufacturing methods, better drug formulations, lower-dose prescriptions and shorter treatment periods are all feasible, safe and potentially effective. Implementation of these efforts would, they say, make the drugs more accessible to the remaining two-thirds of people with HIV disease, most of them living in poor sub-Saharan Africa and unable to afford or get access to treatment on their own.

The new focus is needed, they argue, to counter widespread budget constraints and reluctance on the part of developed nations to contribute much more than the $56 billion already invested in such international aid

programs as the U.S. President's Emergency Plan for AIDS Relief, known as PEPFAR, and the Global Fund to Fight AIDS, Tuberculosis and Malaria. More fiscal belt tightening is occurring despite these programs' proven success during the last decade in dramatically increasing the number of infected people receiving treatment in impoverished sub-Saharan Africa, from an estimated 50,000 in 2003 to 4.7 million today.

"Our biggest challenge in treating those already infected with HIV in the developing world is figuring out how we are going to stretch our existing drugs further to treat two or even three times as many people," says Flexner, "Fortunately, the scientific and chemical engineering evidence is on our side."

In the report, Flexner and his colleagues call for improvements in manufacturing to lower cost of existing drugs, noting that most anti-HIV drugs prescribed in developing nations are generic and already market priced as low as possible. Yearly drug costs for treating HIV disease run between $130 and $1,500 per patient.

Flexner and other experts say that pharmaceutical companies largely refrain from making cost-saving improvements to antiretroviral therapies on their own because any savings from more streamlined drug manufacturing are too small, outweighed by marketing and regulatory costs tied to government approval for any change in production methods. "There's simply no financial incentive for them to make any changes under our current drug pricing structure," says Flexner. "So it is up to the scientific community to step up and fill in the gap."

Flexner says the new report serves as an action plan for the more than 140 scientists, policy experts, philanthropists and pharmaceutical industry representatives who gathered in June 2010 in Alexandria, Va., as part of the first consensus conference on antiretroviral drug

optimization.

The international group puts manufacturing improvements, such as using cheaper suppliers of raw materials or formulation changes to optimize how well drugs are absorbed by the body at the top of the list for lowering the cost of anti-HIV drugs.

One example of this approach, says Flexner, was the emergence in 2007 of a new, competing manufacturer for a raw ingredient used to synthesize tenofovir, the world's most widely prescribed antiretroviral drug and a key component of the widely used combination therapy, Atripla. Using the competitor's product reduced tenofovir's drug price by nearly 60 percent within four years and saved aid programs millions. Changing reagent suppliers and using more advanced technology to manufacture another Atripla drug, efavirenz, has led to a 64 percent drop in the price within the last five years.

Many drugs, Flexner says, such as tenofovir, have a body absorption rate – a measure of how much of the key active chemical ingredient actually gets into the bloodstream – of less than 30 percent. Doubling this, Flexner contends, could save on the number of pills patients need.

He says twice as many people could have access to tenofovir if the average dose needed to effectively treat the disease were lowered to 150 milligrams daily from 300 milligrams daily.

According to Flexner, most drugs are prescribed at slightly higher doses than actually needed to ensure the desired effect. The overdosing doesn't harm people taking the drugs, he says, but it shows how drug manufacturers are "erring on the side of caution, in prescribing more of a drug rather than less," which may be particularly true of antiretroviral medications, whose development was sped along in the past two decades in the rush to fight HIV disease.

Flexner says that lowering the dose of prescription drugs used in treating people in the developing world is perhaps the most controversial of the group's proposals, as "we do not want there to be any possibility of providing substandard care."

Flexner emphasizes that careful research will have to be done to validate any lowering of antiretroviral medication doses, so as to avoid development of drug resistance and to dispel ethical concerns about substandard treatment of people in developing countries. Studies are already under way, he notes, using slightly lower doses of efavirenz and stavudine, especially for slimmer or shorter people in developing countries whose average body mass may not warrant the larger doses.

"Even if two-thirds the daily dose, or maybe even half, works just as well as the initial prescription, millions more people infected with the disease stand a good chance of gaining access to our existing supply of anti-HIV drugs," says Flexner.

And while fewer pills, says Flexner, could lead to better disease management in some cases, scientific teams elsewhere are evaluating the use of add-on pharmacological "boosting" drugs to enhance the effects of active ingredients in other drugs. A black pepper derivative, called piperine, could be used to enhance concentrations of drugs like the integrase inhibitor raltegravir.

Pharmacologists are also, he says, looking to extend the shelf life of anti-HIV drugs as a means of making them more accessible to infected people in the developing world. Such a move would reduce the number of drugs going to waste and allow for less-expensive shipping by sea instead of by airplane, he notes, especially for drugs which might reach their expiration date during transport and delivery.

"All these seemingly small innovations and improvements can add up,"

says Flexner, whose teams have already begun to calculate the costs and benefits of their many attempts at drug optimization.

Flexner says the antiretroviral drug optimization group met in May in Geneva with the United Nation's World Health Organization to work on revamping treatment guidelines for HIV disease to incorporate their optimal drug use strategies.

Provided by Johns Hopkins University