H1N1, Latent Reservoirs and ViiV: 2009 in Review

In honor of World AIDS Day, AIDSmeds highlights the year's top treatment stories.

November 24, 2009 By David Evans

World AIDS Day, held each December 1, is always a time to reflect on how far we've come in the epidemic and how far we have left to go. This year is no different. Fortunately, 2009 was an eventful year in HIV treatment. After nearly three decades since the discovery of the virus, not only are people with HIV surviving longer, many are even thriving on antiretroviral (ARV) treatment.

Of course, the ARVs available aren't perfect, and many people with drug-resistant HIV desperately need new options. There's also lingering debate regarding when HIV treatment should be started, given the growing and potentially avoidable number of non-AIDS diseases among people still in the early stages of HIV disease. And as always, this question remains: What about a cure?

The good news is that we continue to make progress. In honor of World AIDS Day, we decided to summarize the year's top 10 treatment stories as a way to think about the accomplishments we've witnessed and the potential future they promise.

Did other topics catch your eye this year? Did some stories give reasons for hope, or cause you to talk with your provider? Post comments below and continue the discussion.

Pandemic Panic

Within weeks of the first deaths from the H1N1 influenza virus in Mexico in April, then popularly known as "swine flu," global media coverage of the epidemic contained more doomsday scenarios than hard scientific facts. Slowly, a more complete—and accurate—picture of the H1N1 outbreak took form. The overwhelming majority of people infected with H1N1 experience only minor symptoms, with a few notable exceptions: those with pulmonary disease, heart disease and diabetes; children with neurodevelopmental problems; pregnant women; and people with compromised immune systems, including those living with HIV.

"[HIV-positive] individuals are at higher risk for serious complications and hospitalization from H1N1 infection, so get vaccinated against H1N1 influenza," urges Rona Vail, MD, an HIV specialist

at Callen-Lorde Community Health Center. “In our experience, the H1N1 vaccine is well tolerated, while H1N1 illness is not!”

If you haven’t been able to access the vaccine yet, universal precautions should be observed. According to Vail, “You can also decrease your chances of contracting H1N1 influenza by avoiding close contact with sick people where possible, washing your hands often and avoid touching your mouth and nose, maintaining a healthy diet and getting enough sleep.”

As for H1N1 treatment, oseltamivir (Tamiflu) and zanamivir (Relenza) remain effective options—provided that they’re started as early as possible after the onset of symptoms, such as fever, aches and pains, and a sore throat. Fortunately, they do not interact with any medications used as a component of antiretroviral (ARV) therapy.

Consolidate and Collaborate

In April, GlaxoSmithKline (GSK) and Pfizer announced plans to form a joint company focusing specifically on HIV. Both companies planned to bring their existing ARVs into the partnership, along with concerted efforts to bring promising experimental compounds to market. Once the ink on the paperwork was dry, in early November, ViiV Healthcare was launched.

Activists have responded with optimism regarding the new venture. “ViiV Healthcare has pledged to work closely with the community on issues such as drug development and access, and so far they have been doing a pretty decent job,” says Jeff Berry, editor-in-chief of *Positively Aware* and cochair of the Drug Development Committee of the AIDS Treatment Activist Coalition. “It’s now up to us as advocates to hold them to that promise.”

Gilead’s Four-In-One

Atripla, the once-daily three-in-one ARV tablet containing Bristol-Myers Squibb’s efavirenz and Gilead Sciences’ tenofovir and emtricitabine, currently dominates the market for HIV treatment newcomers. Gilead is now looking to go solo with its own fixed-dose combination tablet: a “quad” incorporating its experimental drugs elvitegravir and GS 9350 along with tenofovir and emtricitabine.

Elvitegravir, Gilead’s integrase inhibitor, is in Phase III testing and nearing the approval finish line. GS 9350, a novel pharmacokinetics enhancer in Phase II studies, is Gilead’s possible answer to the low dose of Norvir (ritonavir), which elvitegravir currently requires to maintain effective blood levels.

The four-in-one pill is now being tested in people new to treatment, and results are expected within one to two years. Gilead also plans to make both elvitegravir and GS 9350 available as stand-alone agents to use in combination with other ARVs.

“Both physicians and patients will be looking for treatment options that are simple, tolerable and

with a low incidence of long-term adverse events," predicts the University of Toronto's Sharon Walmsley, MD. "If the efficacy and tolerability of the new 'quad pill' can be confirmed, this may provide many of the factors we strive for. And the compactness of a single tablet makes it very appealing."

Never Too Early?

"The evidence keeps stacking up that antiretroviral treatment should be initiated earlier," comments Matt Sharp, the director of treatment and prevention advocacy at Project Inform.

Sharp is referring to the increasing number of studies showing that people with uncontrolled HIV reproduction appear to be at greater risk of developing a number of health problems, such as cardiovascular disease, brain and nerve damage and some non-AIDS-related cancers. The risk remains even when people have more than 350 CD4 cells (the current suggested start point for ARV treatment).

There has been a great deal of buzz in recent months around the expectation that the Department of Health and Human Services (DHHS) might soon recommend ARV treatment for HIV-positive U.S. residents with CD4s above 350, similar to updated guidelines recently published by the European AIDS Clinical Society. (Editor's note: The DHHS guidelines were amended, in support of recommendations for earlier treatment, on December 1, after this web exclusive was originally published.)

"The big question is whether earlier treatment, maybe very early, might also have an effect on new transmissions in a community," Sharp says, referring to the debate about starting treatment as soon as possible to reduce viral load and, with it, the risk of transmitting the virus to others. "If that proves true, we'll also have to understand what kind of side effects [can be expected in people who] are on antiretroviral treatment that much longer. We'll also have to figure out how we're going to pay for so many more people to be on treatment."

Expanding Options

People with HIV new to treatment got two more ARV options to choose from this year. The integrase inhibitor Isentress (raltegravir), originally approved for treatment-experienced patients in October 2007, was given the green light in July by the U.S. Food and Drug Administration (FDA) for those new to therapy. And on November 20, the FDA also approved the entry inhibitor Selzentry (maraviroc) for treatment first-timers.

Isentress pretty much sailed through the approval process, making a strong showing when compared with Sustiva (efavirenz).

Selzentry's potential for those new to HIV treatment had been less certain. The drug, which only works in people whose virus uses a cell receptor called CCR5 to enter cells, didn't look too potent when trial results comparing the drug to Sustiva were first reported in 2007. A later analysis, this

time using a more sensitive tropism test for detecting whether the virus uses CCR5 or not, showed that Selzentry was probably more potent than it looked at first glance.

It's too early to say where the drugs will fit in the range of ARV options for first-time treatment takers. Further studies will likely determine whether they'll make it onto the DHHS's list of preferred HIV treatments.

Cancer Caution

Of concern, researchers reported several studies this year showing a higher prevalence of certain cancers in people with HIV, compared with their HIV-negative counterparts.

"Several important studies this year have highlighted that although the rate of AIDS-defining cancers such as Kaposi's sarcoma (KS) are declining, the rate of other cancers not traditionally linked to HIV infection are increasing," reports Nancy Crum-Cianflone, MD, of the Naval Medical Center in San Diego. "In fact, most cancers we are seeing today are not AIDS-defining cancers."

Rather, problems such as anal cancer, Hodgkin's lymphoma, lung cancer, liver cancer and skin cancers are topping the list of cancers on the rise among people living with HIV.

Crum-Cianflone says some of the problems arise from coinfection with other viruses such as hepatitis C virus (HCV), along with the increased likelihood that HIV-positive people engage in risky behaviors such as smoking, compared with HIV-negative people.

Fortunately, it looks like people can decrease their cancer risk by doing a number of things—including treating hep C, quitting smoking and perhaps starting HIV treatment earlier.

HPV Vaccine Progress

Vaccines against human papillomavirus (HPV) were big news in 2009, including the approval of a new option to prevent infection, a new use for an older vaccine against the cancer-causing virus and encouraging results using a vaccine with therapeutic potential.

"People with HIV are disproportionately affected by cervical and anal cancers for which the [causative] factor is often HPV," says National Health Services physician Seema Yasmin, MD, from London. HPV, a common infection among people living with HIV, can also cause vaginal, penile and mouth cancers.

In an effort to reduce the number of new cervical cancer-causing HPV infections in women, the FDA approved in October a second preventive vaccine for girls and young women: GSK's Cervarix. The agency also gave its blessing to Merck's Gardasil, originally approved in 2006, to protect against some HPV-related diseases in boys and young men.

Potentially of greater benefit to people with HIV, many of whom are already infected with HPV and won't likely benefit from preventive immunizations is the news of a new type of HPV vaccine that was unveiled in early November. It's a therapeutic vaccine, which means that it is designed to help the immune system control HPV in people who carry the virus. The vaccine was effective in clearing up lesions resulting from one of the most common cancer-causing strains of the virus: HPV type 16.

In the meantime, Yasmin says screening for cervical and anal lesions and treating them early can be key. She says cervical cancer screening in women in London has led to an 80 percent decrease in cervical cancer there. She adds: "There remains a critical need for a structured anal cancer screening program that proactively targets HIV-positive men."

Fat Busters

Unlike the ubiquitous advertisements for questionable "miracle" products that melt inches from your waistline, a proven treatment is on the horizon for HIV-positive people with belly fat accumulation. In June, Montreal-based Theratechnologies filed approval paperwork with the FDA for Egrifta (tesamorelin), a growth hormone–releasing factor that will ultimately be sold by EMD Serono in the United States if it is cleared for approval this spring.

Another fat buster that raised hopes this year is an experimental version of the appetite-regulating hormone leptin. In an encouraging HIV study from the University of California in San Francisco, leptin not only decreased cholesterol and triglyceride levels, but also reduced gut fat by 32 percent—more than twice the reduction seen in clinical trials of Egrifta. Unfortunately, neither researchers nor activists have yet been able to get leptin's manufacturer, Amylin Pharmaceuticals of San Diego, to commit to larger confirmatory studies in people with HIV.

Year of the Integrase

In addition to the encouraging developments involving Isentress and elvitegravir (see above), a second integrase inhibitor, GSK-572, made headlines at the Fifth International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention this summer in Cape Town.

The drug, being developed jointly by ViiV Healthcare and Shionogi Pharmaceuticals, looked impressive in a small 10-day study reported at the conference. Even at the lowest dose tested, people had more than a 100-fold reduction in virus. What's more, a recent analysis of the study indicates that 70 percent of the people on the highest dose, 50 mg, achieved undetectable viral loads after only 10 days on the drug, without using any other ARVs.

GSK-572 moved into larger studies this fall in both treatment newcomers and veterans. And in case GSK-572 doesn't work out, the companies also report that another candidate in the wings looks just as potent.

The Improbable Becomes Possible

News of researchers moving us one step closer to a cure for HIV was clearly a 2009 highlight.

Current ARV therapy can only control HIV—it cannot eliminate the virus completely. That's because a reservoir of inactive CD4 cells harbors latent HIV throughout the body, ultimately archiving the virus for decades. The only way existing ARV drugs can get at this virus is to wake up the long-lived resting cells. Until now, however, no one could figure out how to activate only those cells infected with HIV, and not all inactive cells, which could be deadly. Some researchers, in fact, had declared this endeavor to be impossible.

A team headed by Robert Siliciano, MD, from Johns Hopkins University in Balitmore, has finally developed a way to test drugs that might wake up only those CD4 cells that are infected with HIV. Moreover, a quick first scan of potential compounds revealed nine drugs able to do exactly what was needed. While Siliciano isn't sure that the drugs can be turned into safe treatments for HIV, he remains encouraged.

"This is great news," praises Bob Huff, a longtime treatment activist from San Diego. "Finding a way to look for a new drug can be just as exciting as finding a drug candidate, especially when the target is so elusive and the potential payoff so huge. This is how the integrase inhibitor came into being—it started with the discovery of an assay."

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