United Healthcare to allow HIV/AIDS patients to opt out of mail-order prescriptions

United Healthcare, the nation’s largest health insurer, will allow patients with HIV or AIDS to “opt-out” of a requirement that they obtain their medications by mail order under a national class action settlement announced recently by Consumer Watchdog and Whatley Kallas, LLP.

Due to the complex nature of HIV/AIDS drug regimens, patients rely on their local pharmacists who, working directly with patients, monitor potentially life-threatening adverse drug interactions and side effects. Pharmacists also provide essential advice and counseling that help HIV/AIDS patients and families navigate the challenges of living with a chronic and often debilitating condition.

HIV/AIDS patients also expressed serious concerns about a loss of privacy associated with mail-order.

Under the proposed settlement, patients with HIV or AIDS subject to the mail-order requirement who have privacy or delivery concerns, or who have difficulty discussing their HIV medications over the phone, may obtain their HIV/AIDS medications from an in-network retail pharmacy.

“United should be commended for listening to the serious and heartfelt concerns of their customers who depend on local pharmacists for their life-saving medications,” said Edith Kallas of Whatley Kallas, LLP. “The settlement with United creates a new national precedent for protecting vulnerable patients subject to mandatory prescription drug mail-order programs.”

The list of drugs for which a patient suffering from HIV/AIDS may opt-out of the mail order requirement includes anemia, growth hormone, and neutropenia drugs in addition to drugs used to treat HIV/AIDS.

Class members who paid more for their prescriptions as result of the mail-order requirement may also seek reimbursement of their out-of-pocket costs.

Continued on page 14
There’s a life-saving hepatitis C drug. But you may not be able to afford it.

By Julie Appleby
Kaiser Health News

There’s a new drug regimen being touted as a potential cure for a dangerous liver virus that causes hepatitis C. But it costs $84,000 – or $1,000 a pill. And that price tag is prompting outrage from some consumers and a scramble by insurers to figure out which patients should get the drug — and who pays for it.

Called Sovaldi, the drug is made by California-based Gilead Sciences Inc. and is the latest in a handful of new treatments for hepatitis C, a chronic infection that afflicts at least 3 million Americans and is a leading cause of liver failure. It was approved by the U.S. Food & Drug Administration in December.

"Everyone is still scrambling to figure out how to handle this," said J. Mario Molina, president and CEO of Molina Healthcare, one of the nation’s largest Medicaid managed care companies, which is seeking emergency guidelines from the 11 states in which it operates. "It's far superior to anything we've had to treat hepatitis C. The problem is it's extraordinarily expensive."

Medicaid programs may be particularly hard hit because they are likely to cover a higher proportion of patients with the virus and cannot raise premiums like commercial insurers, Molina said. Medicaid managed care firms like his are paid a set amount per member per month by the state to cover all their medical costs.

If left untreated, hepatitis C causes liver damage over the course of decades. The U.S. Preventive Services Task Force recommends that all baby boomers be tested for the blood-borne virus, which often goes undiagnosed because it produces few symptoms. It is spread mainly by intravenous drug use, but many people were unknowingly infected by poorly sterilized medical equipment and blood transfusions before widespread screening of the blood supply began in 1992. Some may also be infected through tattoos and piercings with contaminated needles.

Big Gains Over Current Drugs
With a success rate of better than 90 percent, Sovaldi is seen as a vast improvement over older treatments, some of which helped only half of patients. Those older drugs cost about $25,000 per treatment, while some newer products approved in 2011 have prices closer to Sovaldi, but have more side effects or are more complex to administer.

A typical course of treatment with Sovaldi goes 12 weeks and costs $84,000, but some patients may need to take the drug for twice as long. Guidelines also suggest that for some patients, Sovaldi be used with other drugs, such as interferon and ribavirin, adding to the cost.

Molina said he has asked state Medicaid directors for guidance on how to proceed with its 2.1 million beneficiaries. In the meantime, he said his firm will not cover the drug, which he says could add $300 million to $400 million to its costs this year. He wants states to cover the drug outside its contracts with his company because the costs were not built into rates negotiated for this year.

Continued on page 4
Interferon-free combo cures 90% of genotype 1 hepatitis C

By Liz Highleyman

An all-oral regimen of daclatasvir, asunaprevir and BMS-791325 – without interferon or ribavirin – led to sustained response in approximately 90% of people with hepatitis C virus (HCV) who had not previously taken treatment, most with hard-to-treat genotype 1a, according to a study presented at the 21st Conference on Retroviruses and Opportunistic Infections (CROI) in Boston during March.

The advent of effective direct-acting antivirals has brought about a revolution in treatment for chronic hepatitis C. New regimens coming through the pipeline will eliminate both interferon and ribavirin, both of which often cause difficult side-effects.

Trevor Hawkins from the Southwest CARE Center in New Mexico reported findings from a trial evaluating an interferon- and ribavirin-free regimen consisting of Bristol-Myers Squibb’s HCV NS5A inhibitor daclatasvir (formerly BMS-790052), the NS3 protease inhibitor asunaprevir (formerly BMS-650032) and the NS5B polymerase inhibitor BMS-791325.

After a pilot study of the triple combination taken for 12 or 24 weeks showed sustained virological response rates of around 90% with either duration at 12 and 24 weeks post-treatment (SVR12 and SVR24, respectively), the researchers conducted an expanded trial to test the 12-week regimens in a larger group of people with genotype 1 HCV infection, including people with liver cirrhosis.

This analysis included 166 people with chronic hepatitis C who had not taken treatment before (treatment naive). About two-thirds were men, about 80% were white and the median age was 54 years. Most (82%) had harder-to-treat HCV subtype 1a, the rest 1b. One-third had the favorable IL28B CC gene variation associated with good interferon responsiveness. Although 20% had advanced fibrosis (stage F3) and 18% had cirrhosis (stage F4) according to the non-invasive FibroTest biomarker index, half that many (9%) had biopsy-proven cirrhosis. People with HIV or hepatitis B co-infection were excluded.

Participants were randomly assigned to receive 30mg daclatasvir, 200mg asunaprevir, and either 75 or 150mg BMS-791325, all taken twice daily for 12 weeks. Although daclatasvir can be taken once daily, in this trial it was taken twice daily to support development of a co-formulation with the other drugs. Prior studies have shown that 60mg once-daily and 30mg twice-daily daclatasvir dosing are equally effective. In an intent-to-treat analysis at 12 week post-treatment, 88.8% of participants in the 75mg BMS-791325 arm and 89.5% in the 150mg arm achieved SVR12. Excluding three people in the 75mg arm and two in the 150mg arm who had missing data, observed SVR12 rates were 92.2% and 91.7%, respectively. The differences between the dose arms were not statistically significant.

In an observed analysis of patient subgroups, cure rates were similarly high regardless of factors traditionally associated with poor response.

For people with HCV subtype 1a, the SVR12 rate was 91% using either the 75 or 150mg BMS-791325 dose. For people with subtype 1b, SVR12 rates were 100% and 94%, respectively. For people with the IL28B CC variant the SVR12 rate was 96% with both doses; for those with unfavorable non-CC variants cure rates were 91% and 89%, respectively.

Looking at people with liver cirrhosis, the observed SVR12 rate was 100% in the 75mg dose arm, but 71% in the 150mg arm (two people with liver cirrhosis in this arm ended up adding pegylated interferon/ribavirin, one due to viral breakthrough and one after stopping BMS-791325). For people who did not have cirrhosis, cure rates were 91% and 94%, respectively. Overall, 13 out of 15 participants with cirrhosis achieved SVR12.

Six people in the 75mg BMS-791325 arm experienced virological failure (two viral breakthroughs during treatment and four relapses after completing therapy), as did five people in the 150mg arm (three breakthroughs and two relapses). All relapses occurred in participants with HCV 1a and happened during the first four weeks of post-treatment follow-up. No factors other than HCV subtype predicted virological failure. Among the 11 people with virological failure, five had evidence of emergent resistance to daclatasvir and asunaprevir and six showed resistance to all three drugs.

Triple therapy was generally safe and well-tolerated. A single participant in each BMS-791325 dose arm discontinued early due to adverse events. There were
Whether we pay for it or the state pays for it, it will be a huge expense," he said. "California spends $3,500 per person a year in the Medicaid program. You could cover an awful lot of people for $84,000."

A Molina spokeswoman said the company is not required to cover the drug since it was approved after its managed care contracts were negotiated. "In the meantime, we are continuing to cover the same medically necessary hepatitis C treatments that were available prior to December 2013," said the spokeswoman, Sunny Yu.

In traditional Medicaid, states must cover FDA-approved drugs marketed by companies that have negotiated rebates with the federal Medicaid drug rebate program. Gilead participates in that program, a spokeswoman said.

But states have flexibility to manage their Medicaid drug costs by using preferred drug lists and requiring prior authorizations for some treatments. In addition, enrollees covered under the health law's expanded Medicaid program may have access to a narrower selection of drugs in some cases, depending on how the state has set up its program.

Limiting How Many Are Eligible
Private insurers, meanwhile, are developing their own criteria for which patients are eligible for the drug, said Steven Pearson, who organized a public forum in San Francisco in March 10 to help patients, doctors, insurers and policymakers compare Sovaldi's cost and effectiveness with other treatments.

Some insurers are limiting it to patients who have tried the older drugs, but failed to get satisfactory results. Others will provide it to those in the middle stages of liver damage, but not to those who show little or no signs of damage, said Pearson, who heads the Institute for Clinical and Economic Review, a nonprofit organization that helps groups evaluate the effectiveness of different medical interventions.

A report prepared for the San Francisco forum estimates that if every patient in California with advanced liver damage were treated, the cost would be $6.3 billion.

Gilead says its price is justified because of the drug's effectiveness. Those who take it can head off chronic problems, such as liver disease or the need for an eventual liver transplant.

"Gilead believes that the price of Sovaldi is fair based on the value it represents to a larger number of patients, including many of those with no current options," said Michele Rest, a company spokeswoman. "The cost of the entire … regimen of 12 weeks of Sovaldi with interferon and ribavirin is consistent with and, in many cases, actually less than the cost of the previous … regimens – with shorter duration of therapy, increased tolerability, and higher efficacy."

She said the company has financial aid programs to assist patients who are uninsured, underinsured or who need assistance to help pay for the medicine, but declined to say how many were enrolled.

What Is The Proper Cost?
In 2011, Gilead paid $11 billion to buy Pharmasset, the company that developed the drug, while it was still in final stage testing. Analysts have estimated that the drug will reap billions in annual sales.

Molina says Gilead is entitled to a return, but questions whether taxpayers should be paying so much of its acquisition costs.

"It is estimated that half the patients who get this will be covered by government programs," Molina said. "If they overpaid for the company they acquired, why should the government have to bail them out?"

Similar questions are being raised by the AIDS Healthcare Foundation, a Los Angeles-based advocacy and health care group, which is urging state Medicaid directors to bargain hard for rebates on the drug's cost.

"The pricing of Sovaldi is being driven by Gilead's desire to recoup its investment in Pharmasset, and assumes it can accomplish this by charging Medicaid and other taxpayer-funded programs whatever it wants," President Michael Weinstein wrote in letters to state Medicaid directors.

Medicaid managed care nonprofit CareSource, headquartered in Dayton, Ohio, says it is already covering the drug, mainly for members who have had bad reactions to the older treatments.

"It's a great medication for the members, but we are concerned about the cost," said Chief Medical Officer Craig Thiele.

Continued on page 5
Patient Advocate Foundation (PAF) recently announced the expansion of its Co-Pay Relief (CPR) program with the opening of the hepatitis C disease silo. Supported through a generous donation of $5 million, this CPR program silo provides financial support for pharmaceutical co-payments for insured patients who are facing financial distress and are unable to afford their costs associated with treatment for the virus.

"Management of hepatitis C is extremely challenging for patients as most need ongoing medication to reduce their chance of liver damage or liver cancer. It is in these cases that a patient’s survival and overall health can be jeopardized if he or she is unable to access pharmaceutical treatment and therapies required to control the virus," said Alan Balch, PhD, CEO of PAF. "We are grateful for the significant support we have received for the hepatitis C silo which allows us to expand our Co-Pay Relief Program in such a meaningful way."

The donation allows PAF to provide financial support to hepatitis C patients ensuring their access to the treatments that can restore balance to their health and markedly improve their quality of life. Qualified patients whose applications are approved are eligible for up to $3,000 per year in copayment assistance through the program.

PAF is a pioneer in the field of copayment support programs, providing more than $190 million in financial assistance to more than 95,000 patients who would have been otherwise unable to afford their pharmaceutical co-payments since 2004. The program provides this support to insured patients who financially and medically qualify, including those covered by government sponsored insurance programs such as Medicare, Medicaid or Tri-care.

For more information about PAF’s Co-Pay Relief program and the options for assistance for hepatitis C patients, visit http://www.copays.org/diseases/hepatitis-c or call (866) 512-3861.

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COTT planning ‘Living Memorial’

By Jeffrey Moualim

Committee of Ten Thousand (COTT) has reached out to the bleeding disorder community for over 23 years, participating in collaborative efforts to benefit those with hemophilia. In recent years, COTT has focused its efforts to build a “living memorial” to those we have lost far too early to HIV/AIDS and hepatitis C, and for the families and friends who remember them today.

The Living Memorial project is not an attempt to rekindle the fires of controversy this tragedy symbolizes, but its mission is rather to celebrate the lives of the men, women, and children we miss every day—people who, through their sacrifice, have made factor VIII and factor IX safer for all of us.

Clotting factor VIII and IX concentrates were developed in the late 1960s and became available for home use in the early 1970s. For people with hemophilia, like me, who were born in the 1950s when only fresh frozen plasma was available to stop bleeding, factor concentrate was a miracle drug: first, to halt a bleeding episode, and ultimately, through prophylaxis, to prevent bleeds from occurring. Immediate infusion of factor minimized joint damage due to hemorrhaging, and led to increased mobility and less pain, so that people with hemophilia could lead a more normal life. Factor concentrates allowed many of us to treat at home instead of visiting emergency rooms every time we had a bleed. And factor opened a world of new possibilities to attend college, travel, and—most of all—become more independent.

Starting in the late 1970s through the mid-1980s, about half of our community became infected with—and many later succumbed to—HIV/AIDS and hepatitis C. Those who survived began a life-and-death struggle. By 1990, with the inception of COTT, a different kind of battle began: a battle for the truth, seeking to expose how factor manufacturers had allowed contaminated plasma to be used in manufacturing factor VIII and IX. The importance of this fight cannot be overstated.

To this day, COTT labors to make sure an accurate history remains, always with the mindset that safety is paramount so that every generation can enjoy the benefits of factor without fear of blood-borne viruses.

The original founders of the COTT board were all infected with HIV, and most were also infected with hepatitis C. Most of them knew that inevitably they would succumb to AIDS or liver failure from hepatitis C. Nevertheless, they made great efforts to ensure that factor products became “cleaner” for future generations.

Though their lives were shortened, their legacy was lengthened, as they became pioneers in blood safety. This legacy included working with government regulatory agencies such as FDA to establish more stringent regulations that protect the blood-product consumer today. As a community, we owe a debt of gratitude to all of these people, living or deceased, for their tremendous commitment and selfless efforts on our behalf to ensure safer factor products.

We must not forget the lessons of the past. COTT is working toward building the Living Memorial to honor those who died, and to give their families and friends a place to visit and reflect on our fallen heroes. The Living Memorial will have greater significance if the entire hemophilia community embraces the idea that all of us—past, present, and future—are in this struggle together, living with hemophilia and remaining vigilant that blood products are safe. Bridges of trust and respect must be built between the generations, because a fragmented community increases the chance of an inadequate response to any potential new crisis.

Although an official site has yet to be confirmed at the time of this writing, we do know that the Living Memorial will be located in San Francisco. Currently, COTT has raised over $10,000 (approximately 5% of what is needed to build the memorial) and we have received a donation in kind from the architectural firm RRM Design Group in San Luis Obispo, California. Under the direction of Eddie Herrera and his team at RRM, the initial renderings of the Living Memorial have been completed at no cost.

If you’re interested in contributing to this valuable and significant project, please visit the COTT website at www.cott1.org to donate and to see the artists’ renderings of the planned Living Memorial.

Jeffrey Moualim is CFO and fund development coordinator of COTT. He was cured of hemophilia through a liver transplant, but continues to help the community. He can be reached at jmoualim@aol.com.

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Risk score can help predict which HIV-affected people have highest risk of kidney disease during tenofovir treatment

By Michael Carter

Investigators in the United States have developed a risk score to predict which people living with HIV have the highest risk of developing chronic kidney disease.

Published in the online edition of AIDS, the risk score is based on the Framingham score used to predict cardiovascular disease risk. The investigators hope their score will help doctors and the people in their care to reach decisions about the use of anti-HIV drugs associated with kidney dysfunction.

Kidney disease is a recognized complication of untreated HIV infection. Certain antiretroviral drugs have also been associated with an increased risk of kidney disease, especially combinations that include the drug tenofovir (Viread also in the combination pills Truvada, Atripla and Eviplera).

Tenofovir is a potent and well-tolerated drug recommended for first-line antiretroviral therapy around the world. To better guide the use of tenofovir, investigators from the US Department of Veterans Affairs sought to develop a scoring tool to predict the individualized five-year risk of chronic kidney disease (CKD) in people living with HIV.

The risk score was based on the records of 21,590 male patients who started HIV therapy between 1997 and 2010.

Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) below 60ml/min/1.73m2.

Older age, elevated glucose, elevated systolic blood pressure, hypertension, elevated triglycerides, proteinuria and a low CD4 cell count were all associated with the development of chronic kidney disease and included in the risk score.

During five years of follow-up, 7.7% of the men taking tenofovir developed chronic kidney disease compared to 3.8% of men taking a combination which did not include tenofovir.

For both tenofovir- and non-tenofovir users there was a relationship between their risk scores and the development of chronic kidney disease.

For non-users, the absolute five-year risk increased from less than 1% for men with a zero risk score to 16% for men with risk scores of nine and above.

A similar relationship between risk score and absolute risk was observed in the men taking tenofovir. Individuals with a score of zero had a 1.4% five-year risk, increasing to a 21.4% for men with the highest risk scores.

Increasing duration of tenofovir use was associated with a higher five-year rate of chronic kidney disease (10.9% for those with over one year of use compared to 4.9% for men with less than one year of use). The increased risk associated with longer duration of tenofovir therapy was found across the range of risk scores.

The investigators used the case of a hypothetical 55-year-old man to illustrate the value of their model when reaching treatment decisions. The man was described as having a normal CD4 count and glucose, no proteinuria. However, he had high blood pressure, hypertension and elevated triglycerides. His total risk score was eight. If he was not taking tenofovir, he had an 11% chance of developing chronic kidney disease over five years; this increased to 19% with tenofovir use.

“Our scoring system allows risk assessment to be quantified, providing physicians and patients with an estimate of the absolute risk of developing CKD and providing a more nuanced algorithm for HIV treatment,” comment the authors. “Our CKD risk score could aid clinicians in designing first-line HIV treatment regimens optimized for safety as well as efficacy.”

Reference

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The 'Boston patients' experience HIV rebound after stem cell transplants

By Liz Highleyman
aidsmap

HIV has re-emerged in two Boston men who under- went experimental antiretroviral therapy interruption after receiving bone marrow stem cell transplants for cancer treatment, Timothy Henrich reported recently at the 21st Conference on Retroviruses and Opportunistic Infections (CROI) in Boston. These cases suggest that a functional cure for HIV will be difficult to achieve if even a small amount of residual virus remains in the body.

Henrich and Daniel Kuritzkes from Brigham and Women’s Hospital first described the Boston patients at the 2012 International AIDS Conference, with more detailed follow-up presented at the International AIDS Society (IAS) meeting last July.

The two men received donor bone marrow containing haematopoietic stem cells, which give rise to all types of blood cells including the CD4 T-cells that harbor HIV. Both men's donors had normal or 'wild-type' stem cells susceptible to HIV infection.

These cases therefore differ from the "Berlin patient," who apparently remains HIV-free seven years after stem cell transplants from a donor with a double mutation (CCR5-delta-32) that makes cells resistant to HIV entry. However, the Boston patients themselves both carried a single copy of the protective mutation.

Also unlike the Berlin patient, the Boston men re- ceived what Henrich called "kinder and gentler" re- duced-intensity chemotherapy conditioning regimens that did not kill off all their original immune cells. This enabled them to remain on antiretroviral therapy (ART) throughout the transplant process.

The transplants were successful and the men's own blood cells were progressively replaced by donor cells. Both men maintained viral suppression after the procedure, and frequent and extensive testing over the next few years showed very low levels of HIV. Not only did plasma HIV RNA remain undetectable, but the virus also could not be found in large volumes of peripheral blood mononuclear cells (PBMCs), lymph nodes or gut tissue using the most sensitive assays.

After the men had been apparently HIV-free for 2.6 and 4.3 years, they and their providers agreed to try an analytical ART interruption to see if the virus would return.

At the 2013 IAS meeting, Henrich reported that the men continued to have undetectable plasma HIV RNA and undetectable integrated HIV DNA in PBMCs after 7 and 15 weeks off ART, raising hopes that the stem cell transplant process might contribute to a functional cure.

But these hopes turned to disappointment when Hen- rich reported last December at the Internation- al Workshop on HIV Persistence that the virus had come back in both men.

The first patient experienced HIV re-emergence 12 weeks into his treatment interruption, while the sec- ond man did not show signs of HIV rebound until he had been off ART for eight months.

Once HIV was detected, both men experienced rapid HIV replication, reaching viral loads in the millions. Both had detectable HIV in cerebrospinal fluid. They also developed symptoms of acute retroviral syn- drome, similar to those sometimes seen when people first acquire HIV.

Both men restarted antiretroviral treatment after viral rebound. One patient had developed a new NNRTI (non-nucleoside reverse transcriptase inhibitor) resistance mutation and switched to a different fully ac- tive ART regimen. Both patients were able to regain viral suppression, their symptoms rapidly resolved, their CD4 counts recovered and they are doing well.

"Allogeneic hematopoietic stem cell transplantation can result in loss of detectable HIV-1 from blood and gut tissue and antiretroviral-free HIV-1 remission for variable duration," but "viral rebound occurred despite a reduction in reservoir size...of at least 3 log10," the researchers summarized.

They suggested that long-lived tissue reservoirs that are inaccessible to testing – perhaps including host macrophages which are replaced by donor cells more slowly than T-cells after a transplant – may have con-
 Protected T-cells persist and proliferate in HIV gene therapy study

By Liz Highleyman

Genetically modified CD4 T-cells lacking CCR5 co-receptors reach high levels in the body and are resistant to HIV infection, potentially enabling people to maintain a low viral load while off antiretroviral therapy (ART), according to the latest reports from studies evaluating Sangamo Biosciences’ zinc finger technology.

Pre-treating patients with the cancer chemotherapy drug cyclophosphamide (Cytoxan) promotes proliferation and activity of the modified T-cells, and people receiving the highest dose saw the greatest reductions in HIV viral load, according to a presentation recently at the 21st Conference on Retroviruses and Opportunistic Infections (CROI) in Boston. A report in the latest issue of the New England Journal of Medicine describes outcomes from the first in this series of trials, including one participant with controlled viral load during an extended ART interruption.

Sangamo developed a technique that uses a zinc finger nuclease to disrupt the gene in CD4 T-cells that controls expression of CCR5, the co-receptor that most strains of HIV use to enter cells.

People with two copies of a naturally occurring genetic mutation called CCR5-delta-32 do not produce this co-receptor and are resistant to HIV infection. A man known as the Berlin patient appears to be free of HIV, seven years after receiving transplanted bone marrow stem cells (which give rise to all blood cells) from a donor with this mutation.

In clinical trials of this approach, samples of CD4 T-cells are collected from HIV-positive participants, treated with the zinc finger protein in a laboratory and allowed to multiply. The modified cells, called SB-728-T, are then re-infused back into the same participant. The idea is that these modified cells – being protected against HIV entry – will persist while normal T-cells are killed off by the virus.

This technique has been tested in several cohorts, including people who have not achieved good CD4 cell recovery despite viral suppression on ART, and people who carry a single copy of the natural CCR5-delta-32 mutation, known as heterozygotes.

Researchers have previously reported that the gene therapy procedure is safe and generally well tolerated. The modified SB-728-T cells proliferate and distribute themselves throughout the body like normal T-cells. Study participants experienced substantial CD4 cell gains and decreased virus levels associated with “bi-allelic” or double-copy gene modification.

Cytoxan pre-treatment

The study presented at CROI by Gary Blick from the Circle Care Center in Connecticut evaluated the effect of “pre-conditioning” with cyclophosphamide prior to re-infusion of modified SB-728-T cells.

The rationale is that killing off some normal T-cells “makes room” for the altered cells. Used in treatment of cancer and autoimmune diseases, cyclophosphamide enhances homeostatic proliferation of transferred T-cells, increases levels of certain cytokines and promotes migration of new T-cells to lymphoid organs.

This open-label dose-escalation study included 12 participants, all but one men. At study entry they had high CD4 cell counts (500-1300 cells/mm3) and undetectable viral load on a stable ART regimen.

Participants received intravenous cyclophosphamide at doses of 200, 500 or 1000mg/m2 given one to three days prior to a single infusion of approximately 10-40 billion modified T-cells. Six weeks later they started an analytic ART treatment interruption. The interruption was planned to last 16 weeks but could be extended if a participant maintained a viral load below 10,000 copies/ml and a CD4 count above 500 cells/mm3.

Study participants showed evidence of extensive engraftment of bi-allelic modified T-cells. Both total CD4 counts and numbers of modified cells increased in a dose-dependent manner, with the largest gains seen in the 1000mg dose group.

Most participants saw their viral load decrease during ART interruption. One patient in the 200mg group and two people in the 500mg group had HIV RNA declines of nearly 1.0 log. One participant in the 1000mg group saw a drop of 1.9 log. This individual remains

Continued on page 15
New NNRTI doravirine matches efavirenz for first-line HIV treatment

By Liz Highleyman
aidsmap

The next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) doravirine (formerly MK-1439) showed potent antiretroviral activity and good tolerability in combination with tenofovir/FTC (the drugs in Truvada) in a dose-finding study presented at the 21st Conference on Retroviruses and Opportunistic Infections (CROI) in Boston during March.

NNRTIs are generally well tolerated and well suited for first-line HIV treatment, but as a class they are susceptible to resistance. Pre-clinical studies showed that Merck's doravirine has a distinct resistance profile and remains active against HIV with common NNRTI resistance mutations including K103N and Y181C.

As reported at last year's CROI, doravirine reduced HIV viral load by about 1.3 log in a seven-day monotherapy study. Doravirine is processed by the CYP3A4 enzyme, but it is neither a CYP3A4 inducer nor inhibitor, so it is not expected to have major drug interaction concerns.

Javier Morales-Ramirez from Clinical Research Puerto Rico reported late-breaking findings from a phase 2b study evaluating the safety and efficacy of various doses of doravirine versus efavirenz (Sustiva) for initial antiretroviral therapy.

This study included 208 treatment-naive people living with HIV from North America, Europe and Asia. More than 90% were men, 74% were white, 20% were black and the median age was 35 years. At baseline, the median CD4 cell count was approximately 375 cells/mm3 and 13% had received an AIDS diagnosis. Study participants were stratified by whether their viral load was above (about 30%) or below 100,000 copies/ml; median HIV RNA was approximately 4.5 log10.

Morales-Ramirez reported 24-week results from part 1 of the study, which will continue for a total of 96 weeks. In this part, participants were randomly allocated into five equal-sized arms receiving doravirine at doses of 25, 50, 100 or 200mg once daily, or else efavirenz once daily, all in combination with tenofovir/FTC.

At 24 weeks, 76.4% of participants taking doravirine had viral load below 40 copies/ml compared with 64.3% of people taking efavirenz. Response rates were similar across doravirine doses (25mg: 80.0%; 50mg: 76.2%; 100mg: 71.4%; 200mg: 78.0%). More than 80% of participants in all treatment arms reached the less stringent virological response threshold of <200 copies/ml.

Both doravirine and efavirenz worked better for people with lower pre-treatment viral load in an ad hoc analysis. For people with <100,000 copies/ml at baseline, response rates (<40 copies/ml) ranged from 83 to 89% with doravirine compared with 74% with efavirenz. For those with >100,000 copies/ml, response rates ranged from 50 to 91% with doravirine vs 54% with efavirenz.

Median CD4 cell gains were 137 cells/mm3 for all doravirine arms combined and 121 cells/mm3 for the efavirenz arm.

Doravirine was generally safe and well tolerated. People taking doravirine were less than half as likely as people taking efavirenz to experience serious adverse events (3.0% across all doravirine arms vs 7.1% with efavirenz) or to stop treatment for this reason (2.4 vs 4.8%). Four people taking doravirine and two people taking efavirenz discontinued due to adverse events considered to be drug-related.

The most common side-effects were dizziness (3.6% with doravirine vs 23.8% with efavirenz), abnormal dreams (9.0 vs 7.1%), diarrhea (4.8 vs 9.5%), nausea (7.8 vs 2.4%) and fatigue (6.6 vs 4.8%). Other central nervous system (CNS) adverse events of interest included insomnia (5.4 vs 7.1%), nightmares (1.2 vs 9.5%) and hallucinations (0.6 vs 2.4%). Overall, 20.5% of people taking doravirine reported at least one CNS side-effect, compared with 33.3% of people taking efavirenz.

People taking doravirine had more favorable lipid profiles and less frequent liver enzyme (ALT and AST) elevations compared with people taking efavirenz.

The researchers concluded that doravirine demonstrated potent antiretroviral activity in treatment-naive...
Novel two-drug maintenance combination works at least as well as triple therapy, setting stage for injectable formulation

By Gus Cairns

An oral combination therapy of two antiretroviral drugs, the non-nucleoside rilpivirine (Edurant, also in Eviplera/Complera) and the new integrase inhibitor GSK1265744 (744), was at least as effective as a standard nucleosides-plus-efavirenz triple combination in keeping viral load undetectable in people taking it. These findings were presented at the 21st Conference on Retroviruses and Opportunistic Infections (CROI) in March.

The dual combination was a maintenance therapy. This means patients did not start on it as their first treatment combination, but switched to it after six months on an NRTI-plus-744 combination, as long as they had a viral load under 50 copies/ml. The reason for this is that there has been a raised risk of early failure in rilpivirine-based combinations in people with high viral loads (over 100,000 copies/ml) in some drug trials, so the idea was not to start the two-drug combination until participants in the study had already achieved virological suppression.

The point of doing this study is explained in its title – the Long-Acting antiretroviral Treatment Enabling study, or LATTE for short. Rilpivirine and 744 remain so long in the body that the potential exists for them to be used as injectable formulations that could be administered once a month instead of taking pills. Now we know they are safe to use together as an oral maintenance therapy, there will be a new trial of them as an injected maintenance therapy. The conference heard on Tuesday how an injectable formulation of 744 was being developed for pre-exposure prophylaxis (PrEP).

The study

In the LATTE study, participants were divided into four groups and for the first six months all the groups took triple combination therapy. The four groups took two NRTIs (either tenofovir/FTC, the drugs co-formulated as Truvada; or abacavir/3TC, the drugs co-formulated as Kivexa/Epzicom) and the third drug was either the NNRTI efavirenz or one of three different doses of 744 (10, 30 or 60 milligrams). If, after six months, participants on this starting therapy had viral loads under 50 copies/ml, then those on 744 exchanged their NRTIs for rilpivirine (25mg). Those taking efavirenz continued taking the two NRTIs.

The results

These results are for the first 48 weeks of the study, i.e. 24 weeks each on the starting and maintenance combinations. The full 96-week results will be presented next year.

There were 243 participants in the study, all but ten of them (96%) men. Thirty-eight per cent were non-white and 16% had an initial viral load over 100,000 copies/ml. Baseline CD4 count averaged 410 copies/mm3. The choice of NRTIs was up to doctor and patient: 69% were taking Truvada and 31% were taking Kivexa/Epzicom.

At week 24 (after six months), 87% of study participants taking 744 plus-two-NRTIs had a viral load under 50 copies/ml, with virtually identical viral suppression rates between the three doses, compared to 74% of people taking efavirenz. The 87% taking 744 (160 out of 181 starting) switched their NRTIs to rilpivirine. Adding in 47 participants taking efavirenz, this meant that there were 207 participants in the maintenance phase of the study.

At week 48, 82% of all participants who started taking 744 (including 24-week dropouts) had a viral load under 50 copies/ml and 71% of participants taking efavirenz. This 11% difference was not statistically significant due to relatively small numbers. The difference was driven entirely by the lower efavirenz viral-suppression results in the first 24 weeks: the proportion of participants who had undetectable viral loads at 48 weeks who continued into the maintenance phase was 94% for efavirenz and 93% for 744.

The lower rates of success for efavirenz in the first 24 weeks were largely driven by discontinuations due to toxicity, particularly this drug’s well-known neuropsychiatric side-effects; 13% dropped out of the efavirenz arm in the first 24 weeks due to toxicity compared with 3% in the 744 arms, and combined with drop-outs due to viral failure, 21% on efavirenz discontinued compared to 8% on 744. The only side-effect that was significantly more common with 744 was headache, which was mainly mild (22% of people taking...
AbbVie '3D' combination cures 99% of genotype 1b hepatitis C

By Keith Alcorn

A 12-week triple combination of direct-acting antivirals developed by AbbVie cured at least 99% of previously untreated people with genotype 1 hepatitis C infection, Prof. Rajender Reddy of the University of Pennsylvania Hospital told the 2014 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston recently.

Only one virologic failure occurred during treatment, no patients relapsed immediately after completing treatment, and the only other ‘treatment failures’ were two patients counted as virologic failures after they did not turn up for 12-week post-treatment monitoring visits.

The results came from the PEARL III study, one of the largest of six phase III studies of AbbVie’s direct-acting antiviral combination. AbbVie is one of several companies racing to develop interferon-free combinations of oral drugs that can cure hepatitis C within 12 or 24 weeks.

These are the first results from AbbVie’s phase III development program to be presented at a scientific conference. AbbVie plans to submit data from the phase III studies early in the second quarter of 2014 for US marketing approval and hopes to gain approval before the end of 2014. European Union approval is likely to follow soon afterwards. The combination will be the first to provide treatment for genotype 1b without the need for interferon or ribavirin, a significant step forward in hepatitis C treatment. Many of the side-effects of hepatitis C treatment are associated with interferon and ribavirin.

Genotype 1b is the most common genotype of hepatitis C globally, and comprises the largest proportion of infections in the European region, Latin America, Russia, Turkey, China and Japan.

The phase III studies compared various durations of treatment with a combination of the HCV protease inhibitor ABT-450 boosted with ritonavir co-formulated with the HCV NS5A inhibitor ABT-267, plus the HCV non-nucleoside polymerase inhibitor ABT-333. These were tested with or without ribavirin, in untreated and previously treated patients, including those with cirrhosis. The completed studies did not include people with HIV and HCV co-infection.

PEARL III recruited 419 previously untreated patients with genotype 1b infection. All participants in PEARL III received the triple combination of direct-acting antivirals (referred to as ‘3D’) and were randomized on a 1:1 ratio to receive ribavirin (n=210) or placebo (n=209). Treatment in PEARL III lasted for 12 weeks.

Approximately half of study participants in the ribavirin arm were women, and a majority of participants in the placebo arm were women (58.9%), an unusually high representation for a study of hepatitis C treatment. 95.2% of participants were Caucasian and 77% were recruited in the European region. The mean age of the study population was around 49 years. The majority of study participants had little or no evidence of liver disease: 67.8% in the ribavirin-sparing arm and 71.4% in the ribavirin arm had F0 or F1 fibrosis. Only 21% of the study population had an IL28B CC genotype, which confers a better response to interferon-based treatment.

Cure rates were extremely high in both study arms. 99% of patients in the ribavirin-sparing arm and 99.5% of patients in the ribavirin arm achieved a sustained virologic response 12 weeks after the completion of treatment (SVR12). One case of virologic rebound occurred at week 10 of treatment, while two patients who achieved a virologic response at the end of treatment were subsequently lost to follow-up. Other than these cases there were no treatment failures. There were no significant differences by baseline characteristics, including IL28B genotype.

Treatment was well tolerated. There were no treatment discontinuations due to adverse events and the most common adverse events reported during the study were headache and fatigue, which each occurred in just over one-in-five patients. Pruritis and nausea were the only adverse events that occurred more frequently in the ribavirin arm. Hemoglobin levels fell below the lower limit of normal in 51.4% of patients in the ribavirin arm compared with 3.4% in the ribavirin-sparing arm, and 9% of participants in the ribavirin arm developed anemia compared to none in the ribavirin-sparing arm. The ribavirin dose was reduced in 9% of patients in the ribavirin arm. All of these patients achieved SVR12.

The study investigators concluded that in patients with hepatitis C genotype 1b, a 12-week course of ABT-450r, ABT-333 and ABT-267 – the so-called ‘3D’ combination – is a highly effective and well-tolerated
Janssen submits new drug application to FDA

Janssen Research & Development, LLC, recently announced it has submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) seeking approval for a once-daily fixed-dose antiretroviral combination tablet containing darunavir, a protease inhibitor developed by Janssen R&D Ireland and marketed as Prezista in the U.S., with cobicistat, an investigational pharmacokinetic enhancer or boosting agent, developed by Gilead Sciences, Inc. (Gilead) for use in combination with other HIV-1 medicines.

Once-daily Prezista is indicated for the treatment of HIV-1 in treatment-naive and treatment-experienced adult patients with no darunavir resistance-associated mutations. Prezista is always taken with and at the same time as ritonavir, a boosting agent, with food and in combination with other HIV medicines. If approved, the fixed-dose combination tablet will be marketed under a new brand name and will, for the first time, offer an additional therapeutic option that eliminates the need to take a boosting agent in a separate tablet with once-daily darunavir.

In June 2011, Janssen announced a license agreement with Gilead for the development and commercialization of a once-daily tablet fixed-dose combination product of darunavir and Gilead's cobicistat. Under the terms of the agreement, Janssen R&D Ireland and its affiliates are responsible for the formulation, manufacturing, registration, distribution and commercialization of the darunavir and cobicistat fixed-dose combination worldwide. Gilead will retain sole rights for the manufacture, development and commercialization of cobicistat as a stand-alone product and for use in combination with other agents.

Press release from Janssen

Continued from page 10

patients, a favorable safety and tolerability profile, and fewer drug-related adverse events compared with efavirenz.

Based on these findings, the 100mg once-daily dose was selected for future development and will be used in part 2 of this study, a dose-confirmation analysis that will enroll an additional 120 participants.

In the discussion following the presentation, Daniel Kuritzkes from Harvard Medical School noted that sometimes it takes longer for viral load to go down in people who start with a high level, so with further follow-up past 24 weeks doravirine may no longer look less effective in such individuals.

Reference

Continued from page 11

744 had headaches compared with 11% taking efavirenz: no participants withdrew from the study for this reason).

These results support a trial of the injectable formulations of rilpivirine and 744 as maintenance therapy (as in LATTE, participants will start on six months of oral therapy).

Reference

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Continued from page 12

treatment that can be administered without ribavirin.

Reference

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Continued from page 1

The lawsuit, filed in June of 2013 in federal court in Orange County and presided over by United States District Court Judge David O. Carter, alleged that United’s mail-order requirement illegally targeted HIV/AIDS patients. Class members will be able to opt-out of the mail-order requirement once they are given notice of the settlement and the court completes its review. Consumer advocates expect the Court’s review to be completed by July.

Press release from Consumer Watchdog

Continued from page 3

a total of three serious adverse events, none deemed related to the study drugs. The most common side-effects were headache (25%), diarrhoea (15%), fatigue (11%) and nausea (10%), with no major differences between dose arms.

"This 12-week, interferon- and ribavirin-free, all-oral 3-DAA regimen achieved SVR12 in >90% of patients despite high prevalence of genotype 1a, advanced fibrosis/cirrhosis, and IL28B non-CC genotypes," the researchers concluded. They added that this was a "well tolerated regimen with low rates of adverse events and treatment discontinuations, regardless of BMS-791325 dose."

The triple regimen is now being studied in the phase III UNITY-1 and UNITY-2 trials, testing a twice-daily fixed-dose co-formulation of all three drugs, using the 75mg dose of BMS-791325. UNITY-1 is looking at people who do not have cirrhosis and UNITY-2 at people with compensated cirrhosis.

Daclatasvir is also currently being tested in people with HIV/HCV co-infection. All three drugs in this combination are CYP3A4 substrates. Drug-drug interaction studies have shown that daclatasvir can be combined with several antiretroviral drugs, in some cases with dose adjustments. Asunaprevir can also be used with several antiretrovirals, excluding HIV protease inhibitors; interaction studies are underway for BMS-791325.

Reference

Everson G (Hawkins T presenting) All-oral combination of daclatasvir, asunaprevir, and BMS-791325 for HCV genotype 1 infection. 21st Conference on Retroviruses and Opportunistic Infections, Boston, abstract 25, 2014.

Continued from page 8

tributed to viral rebound.

Virus detected after rebound was genetically similar, suggesting they were clones of only one or a few residual remaining viruses. This implies that even a few remaining HIV-infected cells may be enough to allow full viral rebound once protective ART is stopped.

Speaking at a community cure workshop preceding the conference, Henrich explained that mathematical models indicate that if only one HIV-infected cell remains, the chance of cure is high. If 10 cells remain, viral rebound could take 10 years. If there are 100 residual cells, rebound could still take up to three years.

While these outcomes are disappointing, they shed further light on HIV persistence and how it might be overcome to enable a functional cure without risky stem cells transplants. To date, it remains unclear what factors contributed to temporary HIV remission in these men, what triggered viral rebound, or why one patient was able to remain off ART so much longer than the other.

The researchers saw no increase in the strength of HIV-specific antibody responses prior to viral rebound. The graft-versus-host reaction — in which donor cells attack host tissues — may have played a role in continued surveillance and clearance of residual HIV-infected recipient cells, the researchers suggested. As reported in a related poster, Henrich said that chemotherapy may play some role, "but by itself it doesn't seem to be doing too much."

"Analytic treatment interruption remains the most reliable measure of viral persistence," the researchers concluded. "Defining the nature and half-life of HIV-1 reservoirs is essential in order to achieve durable antiretroviral-free remission."

References


Continued from page 9

off ART with detectable but low and stable viral load.

The researchers noted that the level of bi-allelic modified T-cell engraftment in people taking the 1000mg cyclophosphamide dose was near levels associated with HIV protection in natural CCR5-delta-32 heterozygous individuals.

Cyclophosphamide was generally safe and well tolerated. Some participants experienced nausea, especially at higher doses, but this was successfully managed with anti-emetic drugs. There were no clinically significant decreases in neutrophils, various white blood cells, red blood cells or platelets.

"Cytoxan conditioning may be a useful strategy to maximize the engraftment and anti-viral effects of SB-728-T adoptive T-cell therapy in HIV subjects and may be an important immunomodulatory chemotherapeutic agent for immunotherapy in HIV," the researchers concluded.

Blick explained at a media briefing that the 1000mg dose appeared to approach the threshold for a functional cure, leading the researchers to look at a higher dose of 1500mg to see if they can push up response rates further without unacceptable toxicity. "We can probably get a functional cure if we get enough engraftment," Blick said.

Extended ART interruption

Data from the first phase 1 trial of the SB-728-T approach in humans were published in the March 6, 2014, edition of the New England Journal of Medicine.

In this open-label proof-of-concept study, Pablo Tebas and Carl June from the University of Pennsylvania and colleagues enrolled 12 people living with HIV who had undetectable viral load on ART. They were divided into two cohorts, one with good CD4 cell recovery on ART (>450 cells/mm3), the other with poor immunological recovery (200-500 cells/mm3).

Participants received a single infusion of approximately 10 billion zinc finger-treated autologous or self-donated T-cells, with 11 to 28% of cells successfully modified (cyclophosphamide was not used in this study). Four weeks later, participants in the first group underwent planned ART interruption, while poor CD4 responders remained on treatment.

The median CD4 cell count rose significantly, reaching a median of about 1500 cells/mm3 from the pre-infusion level of about 450 cells/mm3. After one week, the median concentration of CCR5-modified T-cells was 250 cells/mm3, comprising 14% of circulating CD4 T-cells and 9% of circulating peripheral blood mononuclear cells.

The half-life of modified cells was 48 weeks. Modified cells declined by about 2 cells per day while off ART, compared with a decrease of about 7 cells per day for unmodified cells, showing that altered cells lacking CCR5 had a survival advantage.

Several participants experienced viral load reductions during ART interruption, including one whose HIV RNA became undetectable. This individual was found to be CCR5-delta-32 heterozygous, meaning he naturally had some cells lacking the co-receptor. This participant maintained viral control for 31 weeks without ART and remains off treatment.

The modified T-cells appeared safe in the short term, with just one patient experiencing a transient transfusion reaction with low-grade fever and chills. In summary, this study showed that modified SB-728-T cells persist and appear to have a selective advantage over unmodified cells when exposed to HIV during ART interruption.

A press release issued by Sangamo also noted that the company has developed a new process to deliver the zinc finger nuclease using mRNA instead of an adenovirus vector, which will allow recipients to be retreated if necessary.

References


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Hemophilia Association of the Capital Area
2014 Calendar of Events

May
1  KUWYH Dinner, Sports and Exercise, Gatsby’s Tavern, Alexandria, VA – 6:30 pm. Baxter presenting.
5  Women’s Support Group and Dinner, Tutto Bene Restaurant, Arlington, VA – 6:30 pm
15  Deadline for Price Scholarship
17  Educational Seminar (w/out Annual Business Meeting) – Four Points Sheraton, Downtown, Washington, DC — 1 pm. Followed by tour of Madame Tussauds Wax Museum

June
TBD  Deadline for Getting in the Game Applications
2  19th Annual Golf Tournament – Old Hickory Golf Club
8  Pre-Camp Activity
10  Men’s Support Group and Dinner, Location TBD – 6:30 pm
13-19  Summer Camp at Hole in the Wall Gang Camp, Ashford, CT
16  Board Meeting, 7:00 pm – Location TBD
25  KUWYH Dinner, Persistent Pain, Virginia, Location/Time TBD. Pfizer presenting.

July
7  Women’s Support Group and Dinner, Location TBD – 6:30 pm
23  KUWYH Dinner, Topic TBD, Virginia, Location/Time TBD. Bayer presenting.

August
4  Men’s Support Group and Dinner, Location TBD – 6:30 pm
26  KUWYH Lunch, Topic TBD, DC, Location/Time TBD. Bayer presenting.

September
4  KUWYH Dinner, Transition Children to Independence, Location TBD – Fairfax, VA — 6:30 pm. Pfizer presenting.
8  Women’s Support Group and Dinner, Location TBD – 6:30 pm
9  KUWYH Dinner, Setting Educational Expectations, Virginia, Location/Time. Biogen Idec presenting.
15  Board Meeting, 7:00 pm – Location TBD
18-20  NHF Annual Meeting, Washington, DC (HACA is host chapter)
20  Annual Membership Meeting – at NHF Annual Meeting

All events are free to HACA members. To join or register for an event, contact us at 703-352-7641 or admin@hacacares.org