P.I.Perspective

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Reportback of 2014 Conference on Retroviruses & Opportunistic Infections
In this issue of *PI Perspective*, Project Inform reports on data that was presented at this year's CROI in Boston MA, from March 3–6, 2014.

Having an HIV-positive partner with an undetectable viral load protects gay men too by at least 96%

by David Evans, Director of Research Advocacy

We ask you to read this article to the end, though it is a little longer than normal. The details are important and there are critical issues in regards to personal decision making, prevention practice and legal policies.

A new study presented at the Conference on Retroviruses and Opportunistic Infections (CROI) on March 4 has confirmed that an undetectable viral load in the HIV-positive male partner offers high protection to their HIV-negative male partners from HIV transmission through anal sex, by at least 96% and as much as 100%.

Several years ago, the results of a study called HPTN052 sounded a shot heard around the world. For the first time, in a randomized controlled study, it confirmed that when an HIV-positive person was on antiretroviral (ARV) therapy it meant that they were (at a minimum) 96% less likely to pass on HIV to their HIV-negative partner. When the single case of transmission was excluded, because the positive person hadn't achieved an undetectable viral load, it resulted in 99% efficacy.

As it happens, however, that study was carried out almost solely in heterosexuals who were in mixed HIV-status partnerships and the reported rate of anal sex with an HIV-positive male partner were relatively low. Theoretically, we knew the same was likely true for men who have sex with men (MSM), but we couldn't be certain as anal sex has a much higher probability of transmission than vaginal sex, due to the fragile nature of the rectum compared to the vagina.

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96% less likely to get HIV ...

To explore that further, researchers with the PARTNER study enrolled over 1,100 heterosexual and homosexual couples at 75 sites throughout Europe. Approximately 40% of the couples were mixed-status gay men, and 60% were mixed-status men and women. Seventy percent of women reported condomless vaginal sex with ejaculation and 70% of gay men reported condomless anal sex with ejaculation. Thirty percent of gay male partners reported only insertive anal sex.

In fact, this was a criteria for study entry. The couples had to be together for awhile, the HIV-positive partner had to have had a viral load under 200 copies (most modern tests go down to 50 copies) and they had to have been practicing condomless sex for some time. Also, the HIV-negative partner could not use post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP).

This is a first look at the data from the study, which will be concluded some time next year. On average, the gay male couples had been followed for just over one year and the male/female couples for 1.5 years. In all, the total months of follow-up time for all the couples put together was 16,400 months, which is quite robust. Also, there was a median of 45 condomless vaginal or anal sex acts in all partners each year. It ranges from about 14 to 80 condomless sex acts between the partners.

What's more, sexually transmitted infection (STI) rates were moderately high, with 16% of HIV-positive gay men having an STI during the study, and just under 5% of heterosexual men and women. This stands in at least modest contrast to expert advice, which says that the HIV-positive partner must not have an STD lest they increase their likelihood against passing on HIV to others.

The short version of the story is that some of the HIV-negative partners became infected. However, when the researchers sequenced the genetic code of the viruses of the infected partner they never matched the virus of the primary HIV-positive partner. In other words, people got infected solely by people outside of the relationship. In fact, 34% of the gay HIV-negative men reported outside partners, compared with 4% and 3% of HIV-negative men and women respectively reporting such. In crude terms, this means that a viral load, consistently under 200 copies, protected an HIV-positive person's HIV-negative primary partner essentially every time, which is what the researchers said in the session where the presentation was made.

How much do these study results mimic the real world, however? That is a question that will have to be answered with the remainder of the PARTNER study over the next year or so, as well as an additional study called PARTNER2, which is set to begin this year.

When a statistical analysis was run, they found that an HIV-negative woman who engaged in receptive vaginal sex with ejaculation was at a minimum 98% protected. When they ran the same statistical analysis on gay men who had receptive anal sex with ejaculation the minimum level of protection was 96%.

These results certainly call into question the dogma of HIV prevention of the last 30 years as well as the tragic and draconian laws regarding HIV disclosure that exist in much of the world.

Editor's note: This is the part where we are supposed to tell you not to pay attention to these findings and to still wear a condom every time and to disclose your HIV-status to all partners. That's not a bad thing to do. It protects you from STIs and liability (some of the time), it is courteous and it can afford an easier state of mind.

At Project Inform, however, we understand that sex and romance and intimacy are far more complicated than one simple prevention message and that gay men have known this even in the darkest days of the epidemic. If you are HIV-positive and know it, it is probably still a good idea to disclose your status to your partners or to use condoms for anal sex with partners who don't know your status. These data are not definitive and there is no such thing as 100% efficacy in the real world. That said, these data open new doors for gay male couples and heterosexual couples where HIV status might have stood between them and we applaud the researchers for taking on such a potentially controversial area of research.

hiv PrEP News

Monthly or quarterly injectable PrEP continues to wow researchers

by David Evans, Director of Research Advocacy

A new monthly or quarterly injectable form of pre-exposure prophylaxis (PrEP)—whereby drugs are given regularly to HIV-negative people to keep them uninfected—looks extremely promising. New data in monkeys presented on March 4 at the Conference on Retroviruses and Opportunistic Infections (CROI) continued to show extremely high efficacy in both males and females.

Right now the only medication available for use as PrEP is a pill that contains two drugs (tenofovir DF and emtricitabine) that is marketed as Truvada. Truvada must be taken daily and this dosing schedule has proven to be its Achilles heel. People who can take it daily may have nearly 100% protection, but those who miss lots of doses may not be protected at all. Thus, having a simple injection that is highly protective and that would only need to be given once every 1-3 months is highly desirable and could substantially alter the course of the epidemic globally.

This new drug, called GSK-744 for the moment, can be given both orally on a daily basis and as an injection on a monthly or quarterly basis. So far it's been given to nearly 400 people and appears to be highly safe and tolerable. With the injections, the main complaint has been tolerable pain lasting up to five days.

Two new studies were presented at CROI, one in male macaque monkeys that sought to explore what blood plasma concentrations of the injectable long-acting GSK744 were needed to offer protection from rectal challenges of a hybrid monkey/human version of HIV, called SHIV, and the other was to explore the efficacy of monthly GSK744 on vaginal challenges of SHIV.

In the first study in male macaques, eight were given one dose of GSK744 and four were given a placebo injection. They were all challenged weekly with a dose of SHIV in the rectum that closely matches the amount of HIV present during unprotected anal sex in humans. None of the macaques given GSK744 became infected over the first four weeks of weekly rectal challenges, indicating that a monthly dose in humans might be highly effective. The range of challenges needed to infect the GSK744-treated monkeys was 6 to 17.

In the second study, six female macaques received intramuscular injections of GSK744 once monthly for three months. They were challenged vaginally with SHIV twice a week. Six more macaques received a placebo. After 22 challenges, all six of the GSK-744 treated macaques remained uninfected and for 12 weeks after the last injection. This was despite the fact that concentrations of GSK744 in vaginal tissue was significantly lower than in blood plasma. On the other hand, all six macaques that received a placebo were infected after only four exposures.

These results are incredibly encouraging and it is reported that a Phase IIa safety study will begin in humans this spring. That said, it was noted during the session where the data were presented that cost is definitely going to be an issue that will need resolving. Generic manufacturers have brought the cost of other antiretroviral drugs down considerably for lower income countries. Whether the long-acting GSK744 can be made as cheaply remains to be seen. Prices in higher income countries will also be critical, and will affect the cost effectiveness of expanding the drug for PrEP.

hiv HIV Cure News

Second baby with potential HIV remission found

by David Evans, Director of Research Advocacy

A second baby has now been reported to have undetectable HIV levels due to treatment hours after birth, according to a presentation at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI). Moreover, children treated very early in infection appear to have much smaller reservoirs of HIV than children treated later.

In the summer of 2013, Deborah Persaud, from the Johns Hopkins School of Medicine in Baltimore, made headlines when she announced that an HIV-infected infant from Mississippi, who was inadvertently taken off of antiretroviral therapy at 18 months old, had maintained an undetectable viral load for months. The most sensitive tests have been run and no trace of the virus can be found.

Persaud reported that the baby has now gone for 23 months off of antiretroviral treatment with no detectable HIV RNA, but that trace amounts of DNA can be found. No HIV-specific immune responses can be detected as well. That child began full dose antiretroviral therapy at 31 hours of life. It's first detectable viral load, at that point, was roughly 20,000 copies, but dropped precipitously thereafter.

Likewise, Persaud, reported on a second baby at CROI, treated under similar conditions as the "Mississippi baby," this one in Long Beach, California. There, doctors detected HIV in spinal fluid and blood four hours after birth. The mother, who was not on antiretroviral therapy had a viral load of 138,811. Knowing about the "Mississippi Baby," the doctors gave full dose treatment to the child. While this nine month old infant remains on HIV medications, no HIV can be found. There are no immediate plans to take the child off of treatment.

Persaud is not claiming that either child is cured, rather, she is calling their situation "viral remission," and says only that very early treatment appears to limit spread of the virus.

This was confirmed in Persaud's earlier presentation of virus levels in children who were treated early and have been on HIV treatment for a long time. Persaud's team have examined 154 children. Fourteen of them were treated within their first year of life (average 2.4 months), 53 were treated between 1 and 5 years (22.6 months) and 77 were treated at older than 5 years (67.6 months). On average, all of the children had been on treatment for about 10 years.

The children, who ranged in age from 8 to 20, all have well controlled HIV. Those treated within the first year of life had lower pro-viral DNA than those who initiated therapy after one year. As well, children treated early were far more likely to have an undetectable pro-viral DNA than those treated later, 43% compared to just 11%.

SOURCES:

Persaud D, Deveikis A, Gay H, et al. *Very early combination antiretroviral therapy in perinatal HIV infection: two case studies*. CROI 2014.

Persaud D, Patel K, Koralius B, et al. *Virologic Control by 1 Year of Age Significantly Reduces HIV-1 Reservoirs in Perinatal Infection*. CROI 2014.

hiv HIV Cure News

Learning from failure: virus rebound in transplant patients likely came from tiny pool of infected cells

by David Evans, Director of Research Advocacy

As reported in December the two "Boston patients," whom researchers had hoped were in HIV remission ultimately had a return of HIV several months after stopping antiretroviral (ARV) therapy. Now the scientists are hard at work trying to figure out why, and the culprit seems to be a tiny pool of latently infected cells. Timothy Henrich, MD, offered several further details at this year's Conference on Retroviruses and Opportunistic Infections (CROI).

About a year ago, Henrich, from the Brigham and Women's Hospital in Boston, presented preliminary data on two HIV-positive men who received an HSCT due to persistent cancers in their blood. In one patient, infected during birth, researchers were unable to find HIV in blood or cells more than 4 years post-transplant. In the other patient, infected sexually, the researchers were similarly unable to sequence virus more than 2 years post-transplant. Both men originally carried one copy of a defective gene that slows disease progression and reduces the risk of infection. The new stem cells they received, however, did not have the gene defects. Several months post-transplant, all of the men's original cells had been replaced by the donor cells. Both men were treated for graft versus host disease for a year following the transplant, and intermittently therafter.

Despite looking for HIV DNA and RNA from large volumes of blood and plasma, none could easily be found in the majority of cells analyzed about 9 months following the transplant. Ultimately, both underwent a treatment interruption with a planned resumption of ARV therapy if the virus escalated to more than 1,000 copies and both patients came in every other week for blood draws to detect the potential return of virus. In both cases, the men had a 3-log reduction in their HIV reservoirs post-transplant. Also in both patients, unfortunately, there was a return of virus, into the millions of copies along with symptoms of acute retroviral syndrome, including fever and achiness. Henrich explained that other researchers have predicted that it could take over two to three years for virus to return in the case of a successful transplant and treatment interruption and that his data suggest that minute amounts of HIV were preserved in sanctuary sites within the body.

SOURCES:

Henrich TJ, Hanhauser E, Sirignano MN, et al. *HIV-1 rebound following allogeneic stem cell transplantation and treatment interruption*. CROI 2014. Boston. Abstract 144LB.

Henrich T, Hanhauser E, Sirignano M, et al. *In depth investigation of peripheral and gut HIV-1 reservoirs, HIV-specific cellular immunity, and host microchimerism following allogeneic hematopoetic stem cell transplantation*. 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention, June 30-July 3, 2013, Kuala Lumpur. Abstract WELBA05.

hiv HIV Care News

Is HIV becoming more virulent over time? Study says, yes.

by David Evans, Director of Research Advocacy

The standard wisdom says that people generally have ten years of decent health following HIV transmission before they get sick or die. But what if that information is now incorrect? That is the question that researchers from the CASCADE HIV cohort study tried to answer, when they reported on their research results at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.

In all, they enrolled roughly 16,000 HIV-positive people, most of whom were white and male and diagnosed prior to 2011. In order to have a uniform sample, the researchers excluded Africans, recent seroconverters and children under 15. Cases from 1979–2011 were included.

What they found was that the average CD4 count at the time of seroconversion was about 770 in the 1980s, whereas by 2000 it had dropped to 570. The average viral load once it reached a set point increased from 4 logs to 4.5 logs during the same period of time. Last, and most ominously, the time to loss of CD4 cells appeared to increase from 7 years in 1980 to just 3.4 years by 2004 and the virus seemed to be about .4 logs more infectious.

One important question is how much of this is driven by the virus and how much by the host. It could be that viruses circulating now are more fit and more rapidly progressing. Likewise, it could be that those most resistant to disease progression were infected first, while later waves of infection occurred in those more likely to have disease progression. The authors acknowledged this as well as the fact that older samples had degraded in quality. Nevertheless, this was a sobering presentation.

SOURCE:

N. Pantazis, K. Porter, D. Costagiola, et al. *Temporal Trends in Prognostic Markers of HIV-1 Virulence and Transmissibility*. 2014 CROI.

Combo pill of atazanavir and cobicistat is equal to taking both drugs separately

By Alan McCord, Director of Education

Over the past several years, a new boosting drug called cobicistat has been developed to help maintain blood levels of certain HIV drugs, namely for the integrase inhibitor elvitegravir (Stribild). However, cobicistat (COBI) could also be used to boost protease inhibitors, such as atazanavir (Reyataz, ATV) and darunavir (Prezista), thereby reducing historical reliance on prescribing ritonavir (RTV) as a booster which can cause unwanted side effects for some people. Unlike ritonavir, cobicistat has no anti-HIV properties.

In this Phase 3 study of people reported at the 2014 CROI (Conference on Retroviruses and Opportunistic Infections) in Boston, 48-week results showed that the combo pill ATV+COBI was equal to taking the drugs separately, in terms of safety and food intake. Atazanavir should be taken with a light meal to ensure that proper blood levels are maintained. This study investigated whether the combo pill affected blood levels differently when compared to taking them separately or with various amounts of food.

The complicated study design had 63 HIV-negative participants take the two drugs separately or the combo pill for 7 days each, then switch to the other regimen for another 7 days, while taking a light meal. They then repeated this schedule for another 14 days only without a meal. And then, the final fifth part had participants take the combo pill with a high fat meal. Blood draws were taken throughout.

The results showed that when taken with a light meal (compared to no meal), the combo pill increased blood levels of atazanavir over time by 28% (AUC) and by 42% when looking at the highest point of drug concentration (Cmax). It also increased 35% when measured at 24 hours

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Atazanavir + cobicistat together vs. separately

(C24). When comparing a high fat meal to no meal, blood levels were not significantly different for AUC or Cmax, but a high fat meal increased C24 blood levels by 23%.

There were no differences in side effects between the combo pill and the separate drugs. Common side effects included dizziness, stomach pain, muscle and skeletal pain in the chest and colds. Although total bilirubin increased in 5 people (not unexpected when using atazanavir), no changes in lab markers were considered significant.

The bottom line is that taking ATV+COBI as a combo pill appears to maintain the same blood levels of drug when they're taken separately. And, as with current prescription of atazanavir, the combo pill should be taken with a light meal for maximum benefit. The combo pill should now move into studies in HIV-positive people to ensure effective control of HIV.

SOURCE:

X Tao, et al. *Atazanavir/Cobicistat Fixed-Dose Combination is Bioequivalent to the Separate Agents*. CROI 2014. Boston.

Novel attachment inhibitor may eventually expand the HIV treatment toolbox

By Alan McCord, Director of Education

Promising 24-week results were presented in Boston today at the 2014 CROI (Conference on Retroviruses and Opportunistic Infections) on the development of a novel HIV drug called BMS 663068 that targets a new part of the virus' lifecycle called gp120. This protein is located at the end of receptors on HIV and 068 would prevent its attachment to the CD4 receptor on immune cells.

This dose-ranging study enrolled 251 people who were currently or previously on HIV treatment. Four groups were assigned to take 400mg or 800mg of 068 twice a day or 600mg or 1,200mg once a day, compared to taking boosted atazanavir (Reyataz). Everyone also took raltegravir (Isentress) and tenofovir (Viread).

All participants had a viral load of 1,000 or more (44% had viral loads >100,000) and CD4 counts >50 copies (average ~250, 40% below 200). They were all tested for sensitivity to the three drugs in the study although they had at least one major resistance mutation that ruled out using at least class of drugs. Average age was 40, about 60% were men, and about 63% were non-White.

For those in the four groups who took 068, 78-87% achieved undetectable viral loads by week 24, compared to 86% who took atazanavir. People who started with viral loads below 100,000 typically suppressed their HIV 15-20% more than those above 100,000 across all groups, with the exception of the 068 1,200mg dose that showed about equal suppression regardless of viral loads. All five groups had similar increases in CD4 counts.

The rate of side effects was generally the same across all groups, except for a slightly higher rate of grade 2-4 adverse events on the atazanavir regimen. Four people quit the 068 regimen (although they weren't drug related) while two quit atazanavir. The drug works against HIV whether it uses the R5 or X4 co-receptor on CD4 cells.

The drug will continue to be studied over 96 weeks of treatment.

SOURCE:

J Lalezari, et al. HIV-1 *Attachment Inhibitor Prodrug in Antiretroviral-Experienced Subjects: Week 24 Analysis*. CROI 2014. March 3-6, 2014.

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HIV Care News

New HIV drug doravirine as potent as efavirenz, but with fewer side effects

By Alan McCord, Director of Education

Study data were reported today in Boston at the 2014 CROI (Conference on Retroviruses and Opportunistic Infections) comparing the new NNRTI doravirine (MK-1439) to efavirenz (Sustiva). It found that doravirine dosed once a day suppressed HIV and increased CD4 counts as well as efavirenz did over 24 weeks, but with fewer side effects.

This new compound may eventually find its niche among the other NNRTIs because: 1) it may cause fewer neurological side effects than efavirenz, and 2) it may be effective to use in people with viral loads above 100,000, unlike rilpivirine (Edurant, Complera).

This dose-ranging study compared four groups of 25, 50, 100 and 200mg of doravirine to efavirenz in 208 people new to treatment. Everyone also took Truvada (emtricitabine/tenofovir). The average age of participants was 35 years while 91% were men, 74% Caucasian, 20% Black and 17% Latino. Nearly 13% had had an earlier AIDS diagnosis. All had viral loads of at least 1,000 while 30% had viral loads above 100,000. Average CD4 count was around 395 cells while 11.5% started the study at less than 200 CD4s.

Combining all doravirine dose groups, 76% reached a viral load below 40 copies by week 24, compared to 64% on efavirenz. CD4 counts increased an average of 137 on doravirine vs. 121 with efavirenz.

As for starting viral loads, 86% of those who started doravirine with viral loads below 100,000 became undetectable compared to 74% on efavirenz. For those above 100,000, 66% achieved undetectable viral load on doravirine vs. 54% on efavirenz.

As assessed at week 8, common side effects included dizziness (3.0% doravirine vs. 23.8% efavirenz, nightmares (1.2% doravirine vs. 9.5% efavirenz), abnormal dreams (9.0% doravirine vs. 7.1% efavirenz), and insomnia (5.4% doravirine vs. 7.1% efavirenz). Fewer people stopped the doravirine regimen (7.8%) than did those on the efavirenz regimen (16.3%).

When looking at lab abnormalities, doravirine caused fewer cases of total cholesterol (3.7% vs. 23.7% efavirenz) and LDL cholesterol (3.2% vs. 13.2%). Also, changes in ALTs (4.9%) and ASTs (6.7%) on doravirine were better than on efavirenz (9.5% and 11.9% respectively).

The study will continue to use the 100mg dose of doravirine as it moves forward into phase III.

SOURCE:

JO Morales-Ramirez, et al. *Safety and Antiviral Effect of MK-1439, a Novel NNRTI, (+Truvada) in ART-Naive HIV Infected Patients*. CROI 2014. March 3-6, 2014.

Two-drug regimen works well for people new to HIV treatment, with a couple caveats

By Alan McCord, Director of Education

At the 2014 CROI (Conference on Retroviruses and Opportunistic Infections) in Boston, results from the NEAT 001 study showed that the two-drug regimen of raltegravir (Isentress, RAL) + boosted darunavir (Prezista + ritonavir, b/DRV) worked as well as a three-drug regimen with tenofovir + emtricitabine (Truvada). However, this wasn't the case for people who started with low CD4 counts and high viral loads.

The most commonly prescribed regimens for people starting treatment usually includes two NRTIs — or a NRTI backbone — plus a third drug from another class. Plenty of data show how successful these regimens are, especially with regards to controlling HIV over time. However, NRTIs can cause unwanted side effects in some people, so novel regimens created from the four other classes may be able to achieve the same thing. (Some call these regimens "NRTI-sparing" or "NRTI-free".)

This European study enrolled 805 people into two groups to take either RAL + b/DRV or Truvada + b/DRV.

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Two-drug HIV regimen works well

Average age was 38, 82% were white and 88% were men. Average CD4 count was 330, 4% also had hepatitis C, and none had evidence major resistance mutations.

Three criteria were used for regimen failure: switching drugs before week 32 due to viral load >50 copies, any viral load >50 at week 32 or beyond, and 1 of 3 clinical issues (all-cause death, new or recurring AIDS condition, or any serious non-AIDS condition).

After 96 weeks, CD4 counts improved by 197 cells (week 48) and 267 cells (week 96) for RAL + b/DRV, compared to the Truvada group at 193 and 266 cells respectively. Those who achieved viral loads <50 were 89% on RAL + b/DRV vs. 93% on Truvada.

However, when looking at failure rates related to low CD4 counts, people who started treatment with CD4s <200 did less well on RAL + b/DRV (39% failure) than on Truvada (21%). On this aspect, RAL was inferior to Truvada. Most of these cases were to detectable viral loads at 32 weeks or later. Five people on RAL had major resistance mutations while no one on Truvada developed any.

Additionally, people who started treatment with viral loads above 100,000 also did less well on RAL + b/DRV (36%) than on Truvada (27%). Although this difference seems dramatic, it was not statistically significant probably due to an immunologic overlap — many of these individuals also had CD4s below 200.

Similar rates of common side effects and serious adverse events were seen in both groups. However, kidney function changed less on RAL (+0.9 eGFR change) compared to Truvada (-3.8 eGFR change).

The bottom line is that the NRTI-sparing regimen of RAL + b/DRV was about equal to Truvada in terms of efficacy and safety. However, people with CD4 counts below 200 and especially if they also have viral loads above 100,000 should probably not start out on this regimen.

SOURCE:

F Raffi, et al. First-line RAL + DRV/r is Non-inferior to TDF/FTC + DRV/r: the NEAT001/ANRS143 Randomized Trial. CROI 2014. Boston.

Common statin inhibitor improves hip bone health but worsens insulin resistance

By Alan McCord, Director of Education

Two common metabolic conditions seen in people living with HIV are bone loss and diabetes. HIV itself as well as HIV meds, diet, genetics and aging can all contribute to how they develop over time. In response to this, scientists are searching for ways to prevent possible fractures and diabetic conditions with existing medications.

Study data reported at the 2014 CROI (Conference on Retroviruses and Opportunistic Infections) in Boston showed that the common statin inhibitor rosuvastatin improved bone density in the hip but not in the spine. On the flip side, it also worsened insulin resistance — a condition that can lead to diabetes. This is the first study in HIV-positive people to examine the relationship of taking a statin to alter bone density.

The study enrolled 147 people currently on HIV treatment for at least six months with viral loads below 1,000 copies (75% were <50) and average CD4 counts of 600. Their fasting LDL cholesterol was below 130mg, and they all had higher immune activation by measuring certain inflammation markers. People were excluded if they showed signs of cardiovascular disease, diabetes or history of fractures.

Average age was 46, about 80% were men, and around 30% were Caucasian. About half were on a protease inhibitor regimen while 90% were taking Viread (tenofovir).

For 48 weeks, 72 people took rosuvastatin while 75 took a placebo. At three time points, researchers measured bone density with DEXA scans in three places: spine, hip and trochanter (top of thigh bone). They also recorded markers for diabetes: glucose, insulin and HOMA-IR (insulin resistance).

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Common statin inhibitor good for one thing, not another

Although results showed that spine bone density remained unchanged in both groups, hip bone density did increase by 0.6% on the statin but decreased 0.6% on placebo. Trochanter bone density rose 0.9% on rosuvastatin but fell 0.7% on placebo.

As for changes in diabetes markers, fasting glucose levels rose 8% on rosuvastatin vs. 3.3% on placebo. Fasting insulin levels rose greatly on the statin by 52% vs. 5.5% on placebo. And insulin resistance levels also greatly increased 72% on the statin vs. 14.5% on placebo.

Although this study can't state that all statin drugs would influence similar changes, at a minimum HIV-positive people who take statins should be regularly checked for changes in pre-diabetic conditions.

SOURCE:

GA McComsey, et al. *Rosuvastatin improves hip bone mineral density but worsens insulin resistance.* CROI 2014. Boston.

New effect from a current drug: tesamorelin lowers liver fat in people with HIV and excess gut fat

By Alan McCord, Director of Education

In a presentation at the 2014 CROI (Conference on Retroviruses and Opportunistic Infections) in Boston, tesamorelin (Egrifta) was shown to reduce liver fat in people with HIV. Tesamorelin was approved by the FDA in 2010 for reducing visceral fat (the dense fat that lies below the stomach muscles and around the internal organs) in HIV-positive people. The research team also studied how tesamorelin affected sites of other fat depots, insulin sensitivity and cardiovascular risk markers. Tesamorelin is a human growth hormone (HGH) stimulating factor.

About 1 out of 3 people with HIV have non-alcoholic fatty liver disease or NAFLD — defined as a liver fat content of 5% or more. Other conditions can also cause fatty buildup such as hepatitis C, which is also seen in about 1 out of 3 people with HIV. These conditions are often associated with abnormal levels of blood fats, insulin resistance and cardiovascular disease. They can lead to more serious liver disease such as cirrhosis and liver failure.

This small study followed 50 people over six months: 28 people who took tesamorelin and 22 who took a placebo. Measurements were taken at 2 weeks and at 3 and 6 months.

Average age was around 50 years old, and all participants were on stable HIV treatment and had study-defined visceral fat. Their CD4 counts were >200, fasting blood sugar was <126mg/dL, and creatinine level <1.4mg/dL. The great majority were men (~84%) and white (~67%) while about 16% were current smokers and about 1 out of 5 also had hepatitis C. No one could be using diabetes meds or had recent use of lipid-lowering or HGH drugs.

This study found similar results for reducing visceral fat that was seen in the original studies leading up to FDA approval. These new results showed that liver fat had dropped by 40% in those taking tesamorelin while people on placebo had an increase of 27%. Additionally, the liver enzyme, AST, dropped more for people on tesamorelin compared to placebo when limiting that analysis only to people with starting AST above the study median. Generally speaking, loss of liver fat was more significantly linked to the loss of belly fat.

Tesamorelin is known to affect insulin levels. And although glucose and fasting glucose levels rose within the first couple of weeks on tesamorelin, by study end they were similar to placebo. The presenters believed that by reducing belly fat, glucose and insulin levels likely improved over time, which in turn countered the negative effects of tesamorelin on insulin.

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Tesamorelin lowers liver fat too

Side effects were generally well tolerated and no differences were seen in the rate of side effects between groups. Seven people (5 tesamorelin, 2 placebo) quit by the end of the study due to an adverse event. These were not significant between the groups.

One downside to these results is the return of fat that was seen in the earlier tesamorelin studies: people who eventually stopped the drug saw their visceral fat return. The same effect may be true for liver fat. Larger and longer studies are needed to assess these aspects of the drug.

SOURCE:

T Stanley, et al. *Effects of tesamorelin on hepatic fat in HIV patients: a randomized, placebo-controlled trial.* CROI 2014. March 3-6, 2014.

New treatment option for HIV/HCV co-infected patients doing well in study

By Andrew Reynolds, Hepatitis C Education Manager

At the end of 2013, simeprevir (Olysio, SIM) was approved for treating hepatitis C (HCV) genotype 1 in mono-infected patients, but not for people living with who are co-infected with HCV. The phase III C212 study is designed to examine the safety, tolerability and effectiveness of SIM + interferon + ribavirin in co-infected patients.

The study comprised 106 people, 85% of whom were men. Most participants were Caucasian (82%) and 14% were African American. The average age was 48. Most participants had genotype 1a (82%), and the IL28b breakdown was 27% with CC genotype, 56% with CT and 17% with TT. People with cirrhosis were allowed: a total of 13% enrolled. The vast majority (88%) were on HIV treatment with an average CD4 count of 629.

People were placed in one of three groups. HCV treatment naïve and prior relapse patients were given 12 weeks of SMV + interferon (INF) + ribavirin (RBV), and then 12 more weeks of either INF + RBV or SMV 150mg + INF + RBV, and then an additional 24 weeks of INF + RBV. The option of shortening this round of treatment through response guided therapy was available.

Among those who were prior partial responders, prior null responders or those with cirrhosis (F4), they were given SMV 150mg + INF + RBV, and then 24 additional weeks of INF + RBV. Each of these groups was then followed for another 24 weeks after treatment.

Overall, 74% of participants achieved an SVR12. The results varied across various groups: 79% of treatment naïve patients achieved an SVR12 as did 87% of HCV relapse patients. Within the partial responders, 70% achieved SVR12 but only 57% of null responded.

The IL28b genotype impacted treatment with 96% of CC, 68% of CT and 61% of TT respectively achieving an SVR12. The severity of cirrhosis impacted treatment effectiveness: 80% of those with a Metavir score of F0-F2 achieved SVR12, as did 64% of those with F3-F4. Finally, whether or not a patient was on HIV treatment appeared to impact HCV treatment success: 75% of those on HIV treatment achieved SVR12 compared to 62% who were not.

There were opportunities to shorten HCV treatment through response guided therapy if certain criteria were met. In all, 89% of treatment naïve and prior relapsers were able to shorten therapy to 24 weeks. Within this group, 87% achieved SVR12.

Overall, treatment was very well-tolerated. During the first 12 weeks, 4 people stopped due to adverse events. The most commonly reported side effects were fatigue (41%), headaches (28%) and nausea (26%). Neutropenia, itching and rash were also reported, but none were considered serious.

These results are very promising and look to provide another option for treating HCV in co-infected patients. Only one recent drug — sofosbuvir — is approved for co-infected patients. With over 300,000 Americans living with co-infection, the need for more treatment options is great. This study marks another step in that direction.

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Hepatitis C Care News

New hepatitis C regimen of just six weeks in length cures nearly everyone in difficult to treat population

By Alan McCord, Director of Education

At the 2014 CROI (Conference on Retroviruses and Opportunistic Infections) in Boston this week, results from the SYNERGY study showed that two new 3-drug regimens cured nearly everyone with genotype 1 hepatitis C (HCV) over six weeks of treatment. This regimen shows significant improvement over current HCV treatment that usually includes ribavirin and sometimes interferon, both of which can cause problematic side effects for patients.

This federal NIAID study included 60 people who were new to treatment with a range of fibrosis including cirrhosis. One-third took 12 weeks of a daily combo pill of sofosbuvir (Sovaldi) + ledipasvir while the other two-thirds were split between taking 6 weeks of a three-drug regimen of sofosbuvir + ledipasvir + GS-9669 or sofosbuvir + ledipasvir + GS-9451.

By using three different drugs that each target a different step in the lifecycle of hepatitis C, the researchers hoped this would more quickly reduce HCV viral load while increasing the cure rate. It appears indeed that this is what has happened.

About 72% were male, 88% were Black, 70% had genotype 1a while the rest had 1b, 80% had an unfavorable IL28B genotype (which predicts poorer outcomes), and 30% had advanced fibrosis of stages F3 and F4. However, people with cirrhosis were only included in the 12-week group. People with HIV or hepatitis B were excluded from the study.

The results show that everyone on the sofosbuvir + ledipasvir combo pill was cured (SVR12) while all but one on the other two regimens were cured (SVR12). Liver inflammation levels (ALT and AST) quickly normalized within the first two weeks of starting treatment in all but three people.

No serious side effects were seen, while the most common side effects included headache, fatigue and diarrhea. A few people also showed a higher creatinine level while on treatment. No one stopped taking any of the regimens due to side effects or adverse events.

Moving forward, the researchers will look at a 3-drug regimen given for just four weeks while also including people with cirrhosis in the shorter length 3-drug regimens.

SOURCE:

A Kohli, et al. Combination Oral Hepatitis C Antiviral Therapy for 6 or 12 Weeks: Final Results of the SYNERGY Trial. CROI 2014. March 3-6, 2014.

Treating hepatitis C in HIV/HCV co-infected people: A new option on the horizon

By Andrew Reynolds, Hepatitis C Education Manager

A new HCV protease inhibitor faldaprevir (FDV), recently submitted to the FDA, achieves an SVR12 rate of 72% in HIV/HCV co-infected people. To date, only sofosbuvir has been FDA approved for treating HCV in co-infected patients, so these results offer additional hope and a second option for effective treatment for co-infected people.

Entitled "STARTVerso4", this is one of a series of studies looking at the effectiveness of faldaprevir with interferon (INF) and ribavirin (RBV) in the treatment of genotype 1 in various populations. This phase 3 study included 308 co-infected people, who were put into one of two treatment groups: (1) FDV 120mg + INF + RBV, or FDV 240mg + INF + RBV The majority of study participants were men (81%) and Caucasian (83%). Average age was 47. All participants had either HCV genotype 1a (79%) or 1b (21%). Most participants (85%) did not have cirrhosis but in those who did, 29% had advanced fibrosis (F3/F4). Finally, 78% were treatment naïve for HCV, most were on HIV treatment, and only 4% had never taken HIV meds.

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The overall SVR12 for this study was 72%, with no difference between the FDV 120mg and FDV 240mg groups. Among treatment naïve participants, 69% achieves an SVR12, whereas 83% of prior relapse patients reached an SVR12. Those with the favorable "CC" IL28b genotype achieved an SVR12 88% of the time, whereas those with the "CT" or "TT" ones reached SVR12 64% of the time. Cirrhosis did not appear to have an impact on SVR: 72% without cirrhosis and 73% with is achieved an SVR12. Similarly, there was minimal difference between genotype 1a and 1b, with 71% and 76% respectively achieving and SVR12.

Researchers concluded that the HIV meds used did not have significant drug interactions. While nearly all participants (98%) experienced a medication side effect or adverse event, only 1% of people had to stop faldaprevir while 7% had to stop all medications. The most commonly reported side effects were nausea (37%), fatigue (34%), diarrhea (27%), headache (25%), loss of strength (23%) and loss of appetite (21%). Additionally, 44% of participants were given a grade 3 or higher abnormality on blood work.

As we fully enter the era of "Directly Acting Antivirals", we are witnessing significant advances in HCV therapies, with many more HCV drugs on the horizon for people living with HIV. That said, most of these drugs have only been studied in mono-infected persons. With the recent approval of sofosbuvir for treating HIV/HCV coinfected patients, and this and many other studies underway, the hope is that HIV/HCV co-infected people will be able to reap the same benefits from HCV treatment as mono-infected persons.

New all-oral regimen is possible for people co-infected with HIV and hepatitis C

By Andrew Reynolds, Hepatitis C Education Manager

At the 2014 CROI (Conference on Retroviruses and Opportunistic Infections) in Boston, results from the PHOTON-1 study showed high SVR12 and SVR24 rates for people co-infected with HIV and hepatitis C (HCV). This new all-oral regimen showed minimal side effects and no drug interactions with HIV medicines.

Safe and effective hepatitis C treatments are needed for roughly 300,000 co-infected Americans. These individuals are at risk for more rapid liver disease progression and end-stage liver disease.

In late 2013, the FDA approved the first "directly acting antiviral" or DAA for co-infected patients called Solvaldi (sofosbuvir, SOF). However, the regimen also included interferon, an injected drug with many side effects that is still a barrier for many patients.

Previous research in HCV mono-infected people showed that an interferon-free regimen of SOF + ribavirin (RBV) is safe and effective for certain HCV genotypes. Just as an all-oral regimen is the goal for treating HCV in mono-infected persons, so it is for the co-infected.

PHOTON-1 is an open-label study that included 223 co-infected persons with HCV genotypes 1, 2 and 3. Individuals were given 400mg SOF and a weight-based dose of RBV for either 12 or 24 weeks, depending on genotype and treatment history. Nearly all were on HIV treatment or had CD4 counts >500 cells. People with cirrhosis were allowed in this study but very few enrolled.

Among those with GT1, there were 114 participants, 98% of whom were on HIV treatment. Among them, 82% were male, 32% African American, and 22% Latino/a. These participants were given 24 weeks of SOF + RBV and 76% (87 of 114) achieved an SVR12. Treatment was generally very well tolerated with fatigue, nausea and headaches most commonly reported. Three people had to stop HCV treatment due to adverse events.

Among those with GT2, 85% of the 26 people were taking HIV treatment. As for demographics, 81% were male, 23% African American and 31% Latino/a. These participants took 12 weeks of HCV treatment and 88%

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(23/26) reached an SVR12. The on-treatment HCV virologic failure was limited to 1 person, and no one experienced an HCV relapse after treatment. Fatigue, insomnia and nausea were the most commonly reported side effects, and one one stopped due to adverse events.

A total of 42 patients with GT3 enrolled, and 93% of them were taking HIV treatment. Within this group, 81% were male, 5% were African American and 26% Latino/a. This group also took 12 weeks of HCV therapy, but only 67% (28/42) reached an SVR. HCV virologic failure occurred in 12 people during treatment, and HCV viral relapse occurred in another 12 after treatment had stopped. Side effects were also similar to the GT2 group, with 3 people stopping therapy due to adverse events.

For all participants, regardless of genotype, no drug interactions interfered with either HIV or HCV treatment effectiveness. There was a small drop in the absolute CD4 count, but this is to be expected with ribavirin. There was no change in CD4 cell percentage. Two individuals developed detectable HIV viral load, but in both cases poor adherence to HIV treatment was the cause.

With all of the advances in HCV therapies, we still need to find safe and effective regimens for co-infected persons. With interferon-free regimens on the horizon for HCV mono-infected persons, this study showed comparable results for co-infected persons. Side effects were minimal and manageable, drug interactions were not a problem, and CD4 counts were only mildly affected. This marks an exciting development in treating HCV in people living with HIV.