P.I.Perspective

PROJECT INFORM'S TREATMENT JOURNAL

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Reportback from the 2013 IAS Conference in Kuala Lumpur

In this issue of *PI Perspective*, Project Inform reports on data that was presented at the 7th International AIDS Society Confrence in Kuala Lumpur, from June 30 to July 3.

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HIV Cure News

Potential HIV remission in two transplant recipients

by David Evans, Director of Research Advocacy

Researchers have reported that two HIV-positive men who received stem cell transplants to treat their cancer have no detectable HIV despite interrupting HIV treatment for at least seven weeks. These data, presented Wednesday, July 3 at the 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention in Kuala Lumpur, don't mean — necessarily — that these men have been cured of HIV, but they are very promising and this result has not been seen before.

As reported earlier and published in March in the *Journal of Infectious Diseases*, researchers at Boston's Brigham and Women's Hospital found two HIV-positive men who had undergone stem cell transplants, with the new cells coming from a donor. In contrast to the way that many stem cell transplants were handled in the past, these two men had something called a reduced intensity conditioning regimen before the transplant, meaning that the therapy to deplete their own immune systems to make space for the donor cells was more gentle and did not require the men to go off HIV treatment during the procedure.

The researchers previously reported that no traces of HIV could be found in blood in the men after approximately three years post-transplant. At the IAS confer-

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ence on Wednesday, the researchers reported new data. They have now conducted three additional experiments. First, the researchers took a much deeper look for virus in peripheral blood mononuclear cells (PBMCs) of both patients. None could be found. Second, the researchers took a sample of gut tissue from one of the men and again no virus could be found.

Finally, in what will be the litmus test for any cure-oriented strategy, the researchers had both men stop taking their antiretroviral (ARV) regimens. At this point, one of the men has been off treatment for 7 weeks and the other for 14 weeks. In both cases virus has not rebounded. In fact, it is still undetectable.

While this result is highly unusual and promising, it should be stressed that we cannot yet call these men "cured," despite what some reporters and bloggers will inevitably report. Nevertheless, these results do suggest that both men could manage to remain off HIV treatment for some time to come.

Study offers more details on people who control HIV after stopping ARVs

by David Evans, Director of Research Advocacy

In November 2012 and March 2013, researchers in France reported on 14 HIV-positive individuals who had gone on HIV therapy in early infection and then eventually stopped treatment, without a lasting rebound of the virus. Such individuals, dubbed post-treatment controllers by the principal investigators of the VISCONTI Cohort, have been off treatment now for between 4–10 years without having lasting increases in HIV above 50 copies in blood.

Such individuals aren't "cured" in the most traditional sense, but there is reason to suspect that many will be able to remain off HIV treatment for an untold number of years, perhaps sparing them any residual lasting side effects.

In the most recent update at the conference, another 4 people have been added to the analysis. CD4 counts ranged 544–915, and most had CD4 counts at or above 900. Three of the 18 had a viral rebound after treatment interruption, which was lasting and significant in two. There was no residual virus below 20 to 50 copies (down to 5 copies) in 13 individuals, but some residual virus in five people (median of 45 copies).

Researchers believe that the French patients can't be the only people to have started treatment early and then successfully interrupted treatment. They have now launched a multi-national effort to find other post-treatment controllers.

BIT225 reduces HIV reservoirs

by David Evans, Director of Research Advocacy

Though most studies of HIV eradication have focused on CD4+ T cells, a new study of a therapy called BIT225 has found a reduction in HIV levels in monocyte cells, which help replenish the architecture of lymph nodes and other sanctuary sites where HIV might hide out and build the innate immune response to toxins and pathogens.

A new product from Biotron, BIT225, disrupts the "Viral Protein Unique" (Vpu) of HIV, which helps with the ultimate reproduction and assembly of HIV-infected cells. BIT225 in healthy HIV-positive study volunteers resulted in moderately lower levels of HIV in monocytes compared to those who took a placebo.

A fair amount of those in the BIT224 group stopped treatment due to headaches and nausea. Some experts have posited that macrophages that derive from monocytes will result in an important reservoir of hidden HIV that must be eliminated to make good on cure strategies. This would be one of the first strategies to confront this important potential reservoir of HIV infection.

HIV Care News

American HIV treatment Guidelines get it right

by David Evans, Director of Research Advocacy

United States antiretroviral treatment guidelines for adolescents and adults from the US Public Health Service apparently get it right in terms of the regimens the document deems preferred for first line therapy. Such regimens were more effective than others, based on an Australian meta-analysis of studies of initial HIV regimens.

Frederick Lee and colleagues from the Kirby Institute conducted a meta-analysis whereby they included any legitimate study where a first line regimen was studied in people living with HIV and they then looked at the likelihood of an undetectable viral load following treatment.

What Dr. Lee found was that an integrase inhibitor was significantly more likely to result an undetectable viral load and less chance for treatment failure than a NNRTI, notably efavirenz, or a protease inhibitor (unboosted or not). This confirms the Department of Health and Human Services (DHHS) guidelines recommendation of raltagrevir (Isentress) as a preferred first line regimen. Further, the Guidelines' recommendation of tenofovir DF + emtricitabine (Truvada) as a backbone regimen was also superior to other regimens. Overall, however, average regimen efficacy was just over 60% when all studies were included and just 75% when more recently approved regimens were studied.

It should be noted that the study reached back in time to the late 1990s so a sub-analysis of more recent and more tolerable regimens may not have resulted in exactly the same results, especially if it was limited to randomized controlled trials. Nevertheless, it does appear to validate the expert consultation of the DHHS guidelines committee for preferred drugs in first line regimens.

Switching to etravirine (Intelence) improves levels of blood fats

by Alan McCord, Director of Education

For HIV-positive people currently on treatment who may need help with better controlling their blood fat levels, switching to the NNRTI etravirine (Intelence) may offer them an option. A retrospective British study followed 389 people between 2008–2012 who had switched to etravirine from regimens with efavirenz (Sustiva) or various protease inhibitors.

Most people (88%) had undetectable viral loads and averaged 505 CD4s before the switch. The others had average viral loads of 44,296 and CD4 counts of 300. The most common reason for switching from efavirenz was neurological side effects. The most common reasons for switching from protease inhibitors were gut issues (like diarrhea), drug interactions and concerns about cardiovascular problems. 98% took either Truvada or Epzicom as the NRTI backbone with etravirine.

As for changes in blood fats, people experienced improvements in their various lipid levels. Significant decreases occurred in triglyceride levels, total cholesterol and LDL (low-density lipoprotein) or "bad cholesterol". The HDL (high-density lipoprotein) level or "good cholesterol" also decreased but only slightly, although the ratio of LDL-to-HDL improved.

For those with undetectable viral loads before the switch, 99% continued to be suppressed 6 months after. This high rate continued through 5 years (96–100%), although the study followed fewer people as the years went on. Average CD4 counts increased to above 650 after 3 and 4 years of follow-up.

For those with detectable viral loads before the switch, 61.3% had undetectable levels at 6 months. However, 86 people stopped etravirine due to side effects similar to efavirenz, including 31 who actually had been on efavirenz. Three people who were originally undetectable became detectable while on etravirine.

For people who have high cholesterol and triglyceride levels, switching to etravirine may be an option for them and still stay undetectable.

hiv HIV Care News

Study shows starting treatment earlier reduces HIV reservoir, improves health over time

by Alan McCord, Director of Education

A French study shows that people who start HIV treatment with CD4 counts above 500 had much lower HIV reservoir levels and higher CD4 counts over time than those who started below 500. Researchers followed 309 people from 2005–2012 an average of 3.7 years and grouped them according to their CD4 counts for comparison: 500 and higher, 200–499, and below 200.

CD4 counts and CD4/CD8 ratios were collected at least yearly. Viral loads were also collected from all participants, which measured the HIV DNA in peripheral blood mononuclear cells, or PBMCs. The study sought to find any difference in the amount of HIV DNA over time among the three groups as well as assess whether immune function would normalize over time.

The results showed that the higher the CD4 count over time, the lower the level of HIV DNA. The average CD4 count was highest in the 500+ group at 1,011 compared to 662 and 515 in the other 2 groups. As for average viral load, the 500+ group showed 2.51 log copies in PBMCs compared to 2.78 and 2.91 log copies in the other groups. Similarly, the CD4/CD8 ratio was also better in the 500+ group at 1.25 compared to .88 and .66 in the other groups.

Although there were not equal numbers of people in each of the three groups (30 in 500+, 155 in 200–499 and 124 in <200) and the average years of follow-up per group also varied, these results suggest that starting treatment even in people at or above 500 CD4s can benefit their long-term health.

New integrase inhibitor dolutegravir shows potent suppression with few side effects

by Alan McCord, Director of Education

The new integrase inhibitor dolutegravir showed better suppression of HIV at 48 weeks than raltegravir (Isentress). Other benefits from taking the once-a-day pill included fewer people who had uncontrolled HIV and who had developed drug resistance.

The Argentinian SAILING study included 724 people who were on a failing regimen with a detectable viral load. Everyone showed resistance to two or more classes of HIV treatment, except for integrase inhibitors. Average CD4 count was near 200 and one-third of them had viral load above 50,000.

Half took dolutegravir while the other half took raltegravir, together with no more than two other drugs, at least one of which was still fully active. By week 48, CD4 counts increased about the same between the two groups: 162 (dolutegravir) vs. 153 (raltegravir).

Also, 71% of those on dolutegravir had undetectable viral load compared to 64% on raltegravir (statistically significant). For those who started with viral loads below 50,000, 75% on dolutegravir and 71% on raltegravir were undetectable at 48 weeks (not statistically significant). However, for those who started their regimen with viral loads above 50,000, 62% of those on dolutegravir were undetectable compared to 47% on raltegravir (statistically significant).

Only 1% on dolutegravir developed new integrase inhibitor mutations while 5% did on raltegravir. Both drugs were well tolerated in this study, and very few severe lab abnormalities were reported for either drug.

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Life expectancy for people with HIV jumps 15 years, but not equally for everyone

by Alan McCord, Director of Education

In results from a study by the NA-ACCORD, researchers reported that the life expectancy of HIV-positive people on treatment in North America increased 15.3 years between 2000–2002 and 2006–2007. The study further suggests that a 20-year-old HIV-positive person who is on stable HIV meds is expected to live into their early 70s, which reflects a similar life expectancy of HIV-negative North Americans.

However, certain populations — including women and those who start treatment at a low CD4 count (<350) — showed less robust increases in life expectancy. Other populations such as people of color also did not fair as well, despite modest increases in life expectancy.

The study included 22,937 people, of which 23% were women and 62% were white. The overall life expectancy increased from 36.1 years in 2000–2002 to 51.4 years in 2006–2007. The researchers then estimated that a 20-year-old starting treatment in the latter period could expect to live to 71.4.

They also looked at specific populations. People who started treatment above 350 CD4s saw an increase from 48.8 years to 68.6, while those who started treatment below 350 saw an increase from 31.4 years to 46.9.

Although people of color showed a jump in life expectancy over time (29.7 years to 48.4 years), they still lagged behind men who have sex with men (53.3 years to 69.3) and white people (52.7 years to 56.9). Others, such as injection drug users, showed no improvement over these time periods (29.5 years to 28.8 years).

Study shows low but detectable HIV levels in semen of some men despite being "undetectable" in blood

by Alan McCord, Director of Education

Reflecting the results reported from a few other studies, the French ANRS EP49 study showed that despite having well controlled blood viral load, nearly 1 in 10 HIV-positive men who have sex with men had a low but detectable HIV level in semen at some point.

Researchers took two sets of samples of blood and semen spaced four weeks apart from 157 men who have sex with men. All were on stable HIV regimens and had blood viral load <50 copies for at least 6 months before starting the study. Average CD4 count was 637, and all men were sexually active.

After testing, HIV was detected in 23 samples of semen, at a rate of 7.6%. (From other studies, the average HIV "shedding" rate is about half this in heterosexual men.) Average viral load in semen was 145 copies, within a range of 50–1,475 copies. Although 32 men had at least one asymptomatic STI such as syphilis or gonorrhea, this did not independently predict the viral load found in semen. No one had herpes simplex 2.

The first of two factors that predicted detectable viral load in semen was a current CD4 count below 554 (increased risk 70%). The second was a higher level of HIV DNA (>318 copies/million immune cells) in blood (tripled the risk).

Although a few large studies have shown a greatly lower risk of transmission when the HIV-positive partner is on stable HIV treatment, the virus can still "shed" in other body fluids such as semen. Whether these low quantities of HIV are infectious are still unknown at this time.

hiv HIV Care News

Very long acting treatment (1 dose per month) is moderately well tolerated

by Alan McCord, Director of Education

A new study combining a once-monthly dose of a nanoparticle formulation of a new integrase inhibitor called GSK-744 with a once-monthly NNRTI called TMC-278 was largely well tolerated in healthy HIV-negative people over 134 days.

The study is looking at a new combination of antiretroviral (ARV) drugs that may be particularly useful in people who struggle with adherence, who don't want to take a daily drug, or who want to use the medications for pre-exposure prophylaxis (PrEP). A separate study is underway for those using either drug alone as PrEP. The current study with the combination regimen was to judge safety for use as ARV treatment in people living with HIV.

Four dosing strategies were tested in the study, following a 14-day oral lead-in dose of GSK-744. After the lead-in dose, people received a lead-in sub-cutaneous (subQ) or intramuscular (IM) 800mg dose of GSK-744 followed by one of the following: 1] an IM 200mg dose alone, once monthly for 3 months; 2] a combo dose of 200mg GSK-744 + 900mg TMC-278 IM once monthly for 3 months; 3] a combo dose of 200mg GSK-744 + 900mg TMC-278 subQ for 3 months, or 4] the single large dose of 800mg GSK-744 IM every 3 months.

Levels of the drug in all arms remained above the cut-off of minimal interaction seen with people taking the drugs orally.

There were no serious side effects. The subQ dose resulted in longer-lasting (at least 30 days) nodules of up to 3 centimeters under the skin than the IM dose, but both strategies reported nodules. It is unclear yet what will be the case in terms of side effects and efficacy against HIV over time in those living with the virus.

In all, what this signifies is a potential therapy that might be ideal for people with adherence challenges who are able to keep appointments on a monthly basis.

Novel scoring system in early infection may help predict who should start treatment sooner

by Alan McCord, Director of Education

A non-randomized Swiss study of 290 people showed that using a novel scoring system of six surrogate markers could help establish best practices for starting HIV meds in early infection — an area of HIV care that could use better tools for guiding medical practice. The system, called ARSSS (Acute Retroviral Syndrome Severity Score), may better identify which individuals should start treatment immediately.

Researchers assigned a score to each of 6 surrogate markers: severe nerve-related symptoms (3), in-patient treatment (3), 50yo or older (1), current sexually transmitted infection (1), higher liver enzymes (1), and lower platelet count (1). They then compared total scores to baseline viral load and CD4 count as well as viral set point (>60 days after estimated time of infection).

The overall average score was 2.3 (range 0–10). People with higher total scores had a significantly lower CD4 count and a higher viral load and viral set point. However, in those who had a planned treatment interruption (40 people), this system did not correlate to the viral set point.

The researchers propose that ARSSS could help predict which patients may have a faster progression of HIV disease, thereby pointing to the need for earlier or immediate treatment. Although this is an interesting system to help inform providers and patients on when to start, it needs further study to confirm the accuracy and usefulness of these results.

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HIV / Hep C Coinfection News

High rate of re-infection with hepatitis C seen in HIV-positive gay men

by Alan McCord, Director of Education

Results from a study in London shows a high rate of re-infection with hepatitis C (HCV) in 858 gay men living with HIV. A total of 145 men were followed who had a documented date of an initial HCV infection.

Earlier studies have shown sexual re-infection of HCV in HIV-positive gay men in several large cities, such as New York, Paris, Amsterdam and London. Although hepatitis C is not generally regarded as a sexually transmitted infection (STI), more data are showing this may not be the case for people with HIV and particularly for sexually active HIV-positive gay men. Risk factors for transmission include active STIs, drug use, and types of sex that allows for blood-to-blood contact including unprotected anal sex.

The study covered the years 2004–2012 and found that 1 in 4 men had been re-infected with HCV within two years of either spontaneously clearing the initial infection (1 in 5 men) or successful treatment to it (73% for genotypes 1/4, 100% for genotypes 2/3). Second re-infections also occurred in 8 men.

These data point to two main issues for providers of medical care. First, routine screening for hepatitis C should continue for sexually active HIV-positive individuals even after successful treatment or clearance. Second, enhanced education efforts should occur in this population to highlight the importance of preventing re-infection.

FibroScan can predict risk of liver damage among people with HIV and hepatitis C

by Alan McCord, Director of Education

Researchers from a Spanish study reported on a non-invasive way to measure liver stiffness that may help predict the risk of liver disease progression in people who are co-infected with HIV and hepatitis C. This method, called non-invasive transient elastometry, is known as FibroScan.

Although routine blood work can provide some information on liver health, they are not as accurate as a biopsy. And although biopsies are considered the gold standard of care, they can also present barriers for patients and providers. Therefore, accurate and non-invasive ways to assess liver health are needed since co- infected people are at a higher risk of faster liver damage than are people with hepatitis C alone.

This study followed 297 co-infected people to predict the risk of liver decompensation (when the liver cannot function properly) and death. All had both a FibroScan and a biopsy performed no more than 12 months apart. A total of 225 were men and 275 were on HIV meds. The average CD4 count was 513 and 79% had undetectable viral loads.

The results showed that FibroScan was more accurate at assessing the risk of decompensation than biopsy (7.1% more accurate). As for predicting a person's survival rate, FibroScan offered a similar accuracy as biopsy (although 3.9% more accurate). Although FibroScan was just recently approved by the FDA for use in the US, it is used widely throughout Europe.

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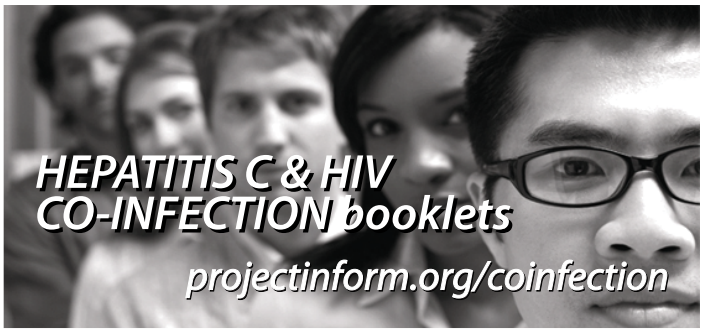

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