P.I.Perspective

PROJECT INFORM'S TREATMENT JOURNAL

STAFF WRITERS
David Evans, *Director of Research Advocacy*
Alan McCord, *Director of Education*

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Reportback from the 2013 ICAAC in Denver, CO

In this issue of *PI Perspective*, Project Inform reports on data that was presented at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy in Denver, CO from September 9–13.

hiv

PrEP (pre-exposure prophylaxis) News

Vaginal ring with tenofovir prevents HIV infection in monkeys

by David Evans, Director of Research Advocacy

In an animal study, five out of six monkeys who were challenged with a monkey and human hybrid version of the AIDS virus were protected when they wore an intravaginal ring with the HIV drug tenofovir. The reason the sixth monkey became infected is unclear. The original monkey kept removing its ring and was eventually replaced by a stand-in monkey that came late into the study.

Either way, these are positive results for a study seeking to understand how alternative delivery methods of HIV-protective medications may be developed and utilized. A vaginal ring may be far preferable and more effective than a gel that must be applied either daily or before and after sex.

In this study, the researchers sought to go one step further by also giving a simultaneous dose of the hormonal contraceptive medroxyprogesterone (Depo-Provera) at relatively high doses. Earlier research had suggested that the contraceptive might negatively affect the preventive efficacy of tenofovir when they're dosed together. In this case, the contraceptive appeared to have no effect on the efficacy of the ring.

The vaginal rings carried a dose of 120mg of tenofovir in the core, and more bio-available tenofovir on the outside of the ring for rapid uptake. The ring achieved the same concentrations intravaginally as a 30mg gel dose.

hiv PrEP (pre-exposure prophylaxis) News

People who use PrEP tend to be women and young people

by David Evans, Director of Research Advocacy

A study by Gilead Sciences of their HIV pill Truvada (tenofovir + emtricitabine) as pre-exposure prophylaxis (PrEP) to prevent HIV infection in HIV-negative individuals reveals that at least half of all users are women and that a substantial proportion of prescriptions come from the southeastern part of the US. The prescriptions also likely came from providers who do not traditionally prescribe antiretroviral therapy for HIV treatment in HIV-positive individuals.

In the study, Gilead sough to drill down on prescriptions where there was only Truvada prescribed — without another anti-HIV pill — and in people who were not diagnosed with hepatitis B virus (HBV) infection. (Truvada is sometimes used to treat that disease in people not simultaneously infected with HIV.)

Gilead estimates that a total of 1,774 individuals received a Truvada prescription for PrEP between January 1, 2011 and the early part of 2013. Prescribing picked up after Truvada was approved for PrEP in the summer of 2012. Gilead found that primary care providers and others who don't typically prescribe HIV medications for HIV-positive individuals were among the top prescribers of PrEP.

Though the number of young people, particularly young men who have sex with men (MSM) — a group at incredibly high risk for HIV infection — remains relatively low in comparison to other groups prescribed Truvada for PrEP, this number nearly doubled over time. It should also be noted that the planned or ongoing PrEP demonstration and implementation research projects may be skewing the results at least somewhat. Nearly all currently open projects are geared toward MSM and transgender females, and this provides full access to PrEP and other services in many urban areas.

hiv HIV Cure News

Functional control of HIV while off treatment possible with cell gene therapy

by David Evans, Director of Research Advocacy

A gene therapy by Sangamo Biosciences produced long-lasting CD4 cell gains in all analyzed participants and lasting viral suppression in two of seven study subjects who received gene modified cells.

The approach by Sangamo is to use an adenovirus to deliver zinc finger nucleases (ZFNs) to the DNA of CD4 cells. The process includes taking CD4 cells from the bodies of people living with HIV, modifying them with ZFN, and then reintroducing them into the same person.

The ZFNs cause a break in the DNA that codes for an important receptor on the cell's surface called CCR5 — a receptor that HIV uses to get into the cells. When the break occurs, about 20% of the CD4s are unable to repair their DNA and therefore go on to become resistant to HIV infection (because they can't produce the CCR5 receptor).

Sangamo has previously reported on other patients receiving infusions of gene modified cells. At this conference, data on seven new patients were reported — all of whom had natural disruptions in one copy of their CCR5 genes. Among these study participants, all patients were treated with the ZFNs and then underwent a 16-week treatment interruption.

Thus far one patient initially had a viral rebound, but then suppressed their HIV through 8 weeks of a treatment interruption. A second patient has now gone about 11 months with very low levels of virus off antiretroviral (ARV) therapy, though virus is still detectable. All five of the other patients had viral rebounds that required resumption of their ARVs by the end of the treatment interruption.

hiv HIV Care News

Full-regimen pills improve adherence and lower rates of hospitalization

by David Evans, Director of Research Advocacy

A regimen containing all the HIV drugs a person needs into a single pill, known as a "single tablet regimen," or STR offered superior adherence benefits to a multi-tablet regimen or MTR and was also associated with fewer hospitalizations.

Not all research into STRs has found a statistically meaningful benefit. However, studies like this are looking at this important issue as more and more STRs are coming to the market. Some are quite expensive. Moreover, it is possible that as generic drugs are introduced, this could lead insurance companies to prefer MTRs over STRs in terms of the cost-sharing associated with those drugs.

In this study, the Veterans Affairs Administration's medical branch looked at the health records of 6,191 veterans who had ever been prescribed an STR and compared their health outcomes to 9,411 veterans who only ever received MTRs. Both groups were very similar in age and other characteristics, though the group taking the STRs was almost twice as likely to have taken their STR medication as first-line treatment than those taking MTRs.

The authors found that veterans taking an STR were about 20% more likely to have 95% adherence — based on refills — than veterans who never took an STR. What's more, veterans receiving STRs were about 9% less likely to be hospitalized compared with those never on an STR. These data can't prove cause and effect, but they are similar to other data from Medicaid databases reported over the past year.

Dolutegravir shows excellent control of HIV among many types of patients

by David Evans, Director of Research Advocacy

The newly approved integrase inhibitor Tivicay (dolutegravir) proved superior to another popular first line regimen, Prezista (darunavir), in a head-to-head study. Improved tolerability and potency in people with high viral loads (over 100,000) appeared to be the largest contributors to the superiority finding.

A total of 484 people were randomized into two groups for 96 weeks: those on Tivicay (50mg) + NRTIs/NNRTIs chosen by the investigators compared and those on with of Prezista (darunavir, 800mg) + Norvir (ritonavir, 100mg) + two NRTIs. The current analysis reported on the results at 48 weeks into the study, which was the primary study endpoint.

In total, 90% of people assigned to the Tivicay regimen had undetectable viral loads across 48 weeks compared to 83% of people taking boosted Prezista. This result satisfied statistical rules such that Tivicay was proved superior to Prezista in terms of efficacy.

Part of the difference in efficacy had to do with tolerability. While 2% of those on Tivicay withdrew from the study for an adverse event, twice as many (4%) withdrew for side effects from Prezista. Similarly, though efficacy rates were almost identical for people who started with viral loads <100,000, in those with higher viral loads (>100,000) Tivicay resulted in undetectable viral loads in 93% compared with just 70% of those on Prezista.

hiv HIV Care News

Stribild as effective as Atripla and boosted Reyataz in older people

by Alan McCord, Director of Education

Results from Gilead's Study 102 and Study 103 showed that the full-regimen tablet Stribild was as effective as regimens with Atripla and boosted Reyataz (atazanavir) in people 50 years of age and older. These 96-week results also showed that they generally responded as well as younger individuals on these regimens.

The results include the following:

	STUDY 102		STUDY 103	
	Stribild	Atripla	Stribild	Reyataz
<50 copies HIV, 50yo & older	82%	82%	90%	90%
<50 copies HIV, under 50yo	85%	81%	82%	81%
drug resistance developed	1	1	0	0
CD4 count increase, 50yo & older	233	250	226	231
CD4 count increase, under 50yo	305	278	261	266
serum creatinine increase, 50yo & older	.14-.16mg	.05mg	.14-.16mg	.12mg
serum creatinine increase, under 50yo	.12-.13mg	.01mg	.12-.13mg	.07mg

In Study 102, older people experienced less dizziness and fewer abnormal dreams while on Stribild, compared to Atripla. In Study 103, no significant differences in side effects were seen between groups. As seen in the chart above, serum creatinine levels increased among those on Stribild.

Stribild contains three HIV meds (elvitegravir, tenofovir, emtricitabine) and a booster drug (cobicistat). Stribild is now listed as a preferred regimen in the Federal Guidelines for people going on treatment for the first time.

New experimental NNRTI called AIC292 looks promising in very early study

by Alan McCord, Director of Education

Data on two different study groups of AIC292 were presented. The first looked at using AIC292 in the lab (in vitro) against wild-type HIV (virus free of resistance) as well as various strains of HIV resistant to the NNRTI class of drugs. In the second group (in vivo), AIC292 was given to mice, to rats and dogs, and to HIV-negative participants.

In vitro, AIC292 showed good activity against both wild-type HIV and strains of HIV that are resistant to NNRTIs. AIC292 also showed better activity against strains with multiple resistance patterns compared to other NNRTIs. Further, AIC292 maintained its potency up to at least one month against these resistant strains.

When AIC292 was combined with other HIV meds, the drug showed a slightly additive or synergistic effect. AIC292 did not appear to have significant interactions with the other HIV meds it was tested against.

In vivo, AIC292 continued to show potent control of HIV consistent with the in vitro studies. No significant side effects were noticed in rats and dogs. In the small group of HIV-negative participants, AIC292 continued to be well tolerated with few side effects, although these were not listed in the presentation.

With this presentation, AIC292 appears to be a promising new NNRTI. Phase II study of the drug will begin shortly.

hiv HIV Care News

Another experimental NNRTI MK-1439 appears to interact with ritonavir, not tenofovir

by Alan McCord, Director of Education

Other presentations at science conferences within the past year have shown the new NNRTI MK-1439 to be a potent HIV medication, with tolerable side effects. At ICAAC this summer, data was presented on its interactions with tenofovir and ritonavir. The blood levels of all these drugs can be affected by a specific protein in the liver, CYP3A4. Therefore, significant drug interactions may result.

Sixteen HIV-negative participants enrolled, with 8 in the MK-1439/tenofovir study and 8 in the MK-1439/ritonavir study. All were men aged 21 to 50.

Both groups were given MK-1439 during a first period of study (length of time not specified by the presentation). A washout period of 7 days followed the first period of MK-1439. Then, the ritonavir group took a daily dose of ritonavir for 20 days, while the other group took a daily dose of tenofovir for 18 days. On day 14 in both groups, MK-1439 was also taken.

Plasma samples were collected after each period to measure blood levels of the three drugs and subsequent interactions. No serious clinical or lab side effects were seen, however, most of the participants reported one or more mild-to-moderate side effects.

As for MK-1439/tenofovir, the combination does not appear to cause any meaningful affect on blood levels of the drugs. However, MK-1439 and ritonavir do interact to a small degree. Ritonavir affected MK-1439 blood levels a small amount but had a significant effect on how quickly MK-1439 clears from the body.

As MK-1439 moves forward in clinical study, combining it with tenofovir doesn't appear to be an issue. However, it's not clear at this time if there's a need for dose adjustments when it's taken together with ritonavir.

New form of tenofovir appears less toxic on bones and kidneys

by Alan McCord, Director of Education

In this study (GS-US-292-0102), 48-week results were reported on comparing the new form of tenofovir (tenofovir alafenamide, or TAF) to the widely used current form (tenofovir disoproxil fumarate, or TDF). In earlier study, TAF has shown higher levels within cells and lower levels in plasma at a smaller dose than TDF. This may mean fewer side effects from tenofovir, including those related to bone and kidney health.

A total of 170 people new to treatment were randomized 2:1 to take either TAF or TDF once a day, along with the other three drugs found in Stribild (emtricitabine, cobicistat, elvitegravir).

The average CD4 count was 390 while average viral load was 40,000. Most participants were men, about 2/3 were white and about 1/3 were black. All had normal kidney function, and no one had current hepatitis B or C. Regular blood work was taken and DEXA scans for bone density were done at 24 and 48 weeks.

Some of the 48-week results include the following:

	TAF	TDF
CD4 count increase (not significant)	177	204
<50 copies HIV	88.4%	87.9%
didn't achieve <50 copies HIV	6.3%	10.3%
developed resistance mutations	0	2
stopped due to lack of efficacy	0%	3.4%
stopped due to side effects	3.6%	0%
nausea	21%	12%
kidney change (eGFR)	-5.5mg	-10.0
kidney change (proteinuria)	2.7%	5.2%
kidney change (serum creatinine)	0.9%	3.4%
bone density change, spine	-1.00	-3.37
bone density change, hip	-0.62	-2.39
bone formation change	109%	169%
bone resorption change	119%	178%

hiv HIV Care News

Fewer neurological side effects when switching from Atripla to Complera

by Alan McCord, Director of Education

A British study looked at the efficacy and safety of switching to Complera from Atripla to see if people experienced fewer neurological side effects. Efavirenz, one of the three drugs in Atripla, can cause significant nerve-related side effects in many people. Given they're both full-regimen pills taken once a day, this may make Complera a better choice for some people. Atripla is currently a "recommended" regimen and Complera is an "alternative" option in the Federal HIV Treatment Guidelines for people going on treatment for the first time.

The 12-week study looked at adverse events at week 4 by assigning scores to reported side effects as well as conducting a sleep questionnaire. At week 12, both were conducted along with assessing viral load, CD4 count changes and changes in fasting lipids. Forty men were enrolled with an average age of 47. Average CD4 count was 640 and all were currently on an efavirenz regimen.

The following results show reductions in side effects (proportion of people reporting symptoms) after switching over to Complera:

	STUDY START	WK 4	WK 12
any symptom	98%	38% (p<0.001)	51% (p<0.001)
dizziness	69%	28%	36%
depression	85%	52%	64%
trouble sleeping	83%	47%	61%
Anxiety	85%	55%	59%
confusion	50%	27%	36%
headache	37%	40%	46%
sleepiness	83%	45%	54%
aggressive mood	55%	30%	46%
abnormal dreams	85%	52%	51%

Despite the small number of people in this study, Complera showed a significantly lower rate of neurological side effects than Atripla, at 4 and at 12 weeks. Everyone maintained undetectable viral loads after switching. Although average CD4 counts dropped a little to 584 by week 12, this was not statistically significant.

New data may influence screening for HPV infection and anal dysplasia

by Alan McCord, Director of Education

Two Spanish studies presented results on HPV infection in men who have sex with men (MSM) and in women. Both anal dysplasia (abnormal anal cells due to HPV) and anal cancer occur more often among people with HIV, especially among MSM (33 times higher risk). HIV-positive women are also at a higher risk (14 times). Therefore, knowing how to predict these serious conditions could help with preventing unnecessary disease and invasive medical procedures.

The first study (conducted from 04/2010 to 09/2012) looked at the risk factors for developing grade 2/3 anal dysplasia or cancer in MSM. The study assessed using various tests to identify cancer-causing HPV strains (PCR) and abnormal anal cells (Pap smear, anoscopy, and both).

A total of 103 people were followed, with an average age of 36. Most participants (85%) were on HIV meds, nearly 40% had anal warts, and nearly half smoked (a risk factor for HPV infection and dysplasia).

Results showed that 9.7% had grade 2/3 anal dysplasia and 10.7% had anal cancer. Although older age and HPV types 6, 39 and 42 were associated with higher risk in one type of analysis, a more comprehensive analysis found that having HPV 39 alone was associated with high grade lesions and cancer.

The study also found that using PCR with Pap smear helped find patients at higher risk for dysplasia. If both tests were normal or negative, then the researchers suggested

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that performing an anoscopy could be avoided altogether and anoscopy-guided Pap smears may not be needed.

The second study (conducted from 12/2008 to 12/2012) looked at the rate of anal dysplasia and risk factors in 45 women and compared those with rates seen in the same 103 MSM detailed above. The women were 43 years old on average. Average CD4 count was 692 while 93% were on HIV meds. Many more women smoked (71%) while fewer had anal warts (22%).

Generally speaking, the incidence of anal HPV disease is lower in HIV-positive women than MSM. The researchers stated, however, it's high enough to make anal HPV screening routine in women with HIV. The only associated factor with anal HPV disease in women was the presence of genital warts, which raised the risk by 11 times.

New link discovered between depression and detectable HIV in brain fluid

by Alan McCord, Director of Education

Depression occurs more frequently in people with HIV, and earlier study shows a link between depression and poorer control of HIV as well as faster disease progression. Although HIV regimens have greatly reduced the rates of brain-related conditions over the years, depression continues to persist in the HIV community.

Results from a new study at Johns Hopkins University show that people with major depressive disorder (MDD) are more likely to have detectable viral loads in their cerebral-spinal fluid (CSF). Where this study differs from earlier study is considering the link between detectable HIV in CSF and undetectable viral loads in blood.

The study included 803 people. Average CD4 count was 445 and average nadir CD4 was 149. Average age was 46, most were men (81%), 41% were white, 46% were black and 13% were Latino or other race. Half stated they had a history of depression. Three or more spinal taps were done on 212 people who did not have detectable HIV in their CSF at study entry.

The prevalence of CSF viral load at study entry was 17.6%. Among people with MDD, detectable CSF HIV was 25.7% compared to 16.3% without MDD. Over the 18 months of the study, detectable CSF viral load occurred in 26.1% of those with MDD compared to 15.1% of those without. The overall rate of detectable HIV in CSF was three-times higher in people with MDD. No differences in blood viral loads were seen.

These results point to the need for increased and careful assessment of depressive conditions in people with HIV. Treating depression may improve long-term HIV disease progression.

hcv

Hepatitis C / HIV Coinfection News

Treatment outcomes of hepatitis C genotypes 2 and 3 in co-infected people similar to mono-infected

by Alan McCord, Director of Education

Little is known about the effect that HIV infection has on the treatment of hepatitis C (HCV) genotypes 2 and 3 in people living with both viruses. An Italian study provided results from a study of 740 people living with these genotypes.

The study compared 113 co-infected people to 627 who were HCV mono-infected. In the study, average age was 45, 67% were men, 33% were women, and 56 had a cirrhosis diagnosis. All were given a regimen of peg-interferon + ribavirin. The co-infected individuals were all taking HIV medications, had undetectable HIV levels, and CD4 counts averaged 455. Most people (95%) had genotype 3.

Although the overall rate of SVR (sustained virologic response, or HCV cure) was 66%, only 58% of co-infected people had an SVR, compared to 67% of mono-infected people. Around 15% of both groups did not respond to the regimen (non-responders), and a few more co-infected (50%) had their HCV return after SVR than did mono-infected (45%).

Factors that contributed to poorer treatment outcomes included the early stop of peg-interferon and a reduced dosing of ribavirin. A higher baseline platelets count was associated with better outcomes.

Although an SVR is not improbable for many co-infected people, these results show some of the difficulty with treating hepatitis C infection in people with HIV. For those who can wait, the newer HCV regimens that are coming to market over the next few years may offer hope of a higher rate of SVR, perhaps without the need for using peg-interferon.

Successful interferon-based treatment greatly lowers liver disease and death in co-infected

by Alan McCord, Director of Education

People who are co-infected with HIV and hepatitis C (HCV) have particular challenges when it comes to reaching effective treatment outcomes for their HCV infection. Treating HCV genotypes 2 and 3 in hopes for a cure has a higher rate of success. People with genotypes 1 or 4 have a much lower cure rate. Beyond that, co-infected people may benefit from hepatitis C treatment in other ways, such as improved liver health, slower HIV disease progression, and lower rates of death.

The Spanish GESIDA Cohort Study followed 695 co-infected people with genotypes 1-4 to see the effects from using interferon-based treatment on liver health and death. It focused on people with less advanced stages of fibrosis (F0 to F2 scores): 11% were F0, 42% were F1, and 47% were F2.

Overall, 39% of the people achieved an SVR. However, people with types 2 or 3 were four times more likely to be cured than those with types 1 or 4. Other known factors also influenced better treatment outcomes: low HCV viral load before treatment and low or no alcohol use.

After 6 years of study, the following results show the improved health outcomes between people with and without an SVR, per 100 person years. These results were confirmed for people with F2, but not F1 or F0.

	SVR	No SVR
progression to AIDS	0.13	0.55
liver decompensation	0.26	0.84
liver cancer	0.13	0.0
liver-related death	0.0	0.09
any death	0.39	0.63

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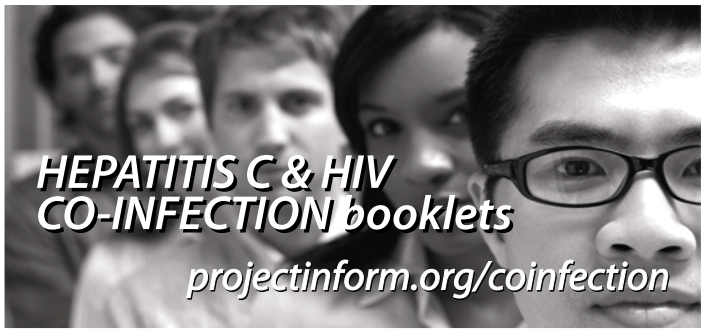

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