

PI.Perspective



PROJECT INFORM'S TREATMENT JOURNAL

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P.I. PERSPECTIVE | MARCH 2015 | 273 NINTH STREET, SAN FRANCISCO, CA 94103 | WWW.PROJECTINFORM.ORG

Reportback from the 2015 CROI (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 Seattle WA, from February 23–26, 2015.

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Pre-Exposure Prophylaxis News

Daily PrEP reduces HIV infections by 86% in U.K. PROUD Study

By David Evans, *Director of Education*

A study of immediate versus deferred daily pre-exposure prophylaxis (PrEP) with Truvada (tenofovir/emtricitabine) in the United Kingdom has found that PrEP may reduce the risk of HIV infection by 86% among men who have sex with men (MSM). The results from the study, called PROUD, were presented on February 24 at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle.

The study, which randomized 545 MSM to start PrEP right away or to wait 12 months, was designed to figure out whether men's sexual activity changed if they knew they were taking PrEP and to see how well PrEP might work in a more typical clinic setting. Last year, the researchers announced that the safety monitoring board had recommended that the participants in the deferred

arm of the study be offered PrEP, because the difference in HIV infections between the two arms was so great. At the time, however, the precise difference in efficacy was not provided.

In short, those taking PrEP were highly protected, their adherence was very high, side effects were no worse than has been seen in previous trials, sexual behavior and sexually transmitted infections (STIs) did not change over time and there was drug resistance was rare. Further details are below.

Efficacy and incidence

One of the reasons that the study was modified at such an early time point is that the researchers had assumed that the rate of new infections would be about 2 to 3%

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Pre-Exposure Prophylaxis News

per year. This was based on clinic other U.K. data from previous years. In fact, the incidence in the deferred arm was 8.9%, roughly three times higher than expected. The incidence in those offered PrEP immediate was 1.3%, resulting in a reduction in infections of 86%. In all, 22 participants became infected with HIV during the randomized portion of the study, 19 in the deferred arm and 3 in the immediate arm.

Adherence

Adherence was measured in three ways; self report, refills and in drug blood levels in 57 participants. Reported adherence was very high, and 56% were prescribed enough pills to match 100% adherence. In the subset with drug level monitoring, reported adherence was matched with drug detection.

Drug resistance

Drug resistance was rare. Among the six who were known or suspected to have been HIV-infected when they started PrEP, three developed drug resistance. As with other studies, they developed resistance to emtricitabine and none had resistance to tenofovir.

Side effects

Of the 30 people who stopped PrEP, only 13 were determined to be consistent with drug side effects and 11 of them were able to resume therapy without a problem. Side effects were similar to that seen in other PrEP studies.

Sexual behavior and STIs

As would be expected from the very high incidence in the deferred arm, sexual risks were high and common. Prior to being randomized to the immediate or deferred arms, sexual behavior was assessed by self-report. The average number of anal sex partners in the 90 days prior was 10, with at least two to three being condomless receptive sex and three being insertive. During the study, there was no significant increase in condomless sex and there was no statistical difference in sexual behavior between the two arms. There was, however, a numerical increase in the number of participants who had high numbers of condomless sex partners and further data will be needed to determine whether this will turn out to be significant.

STIs were also very common. Roughly half were diagnosed with an STI at the start of the study and this number persisted throughout the study and remained statistically the same between the two groups after randomization.

Lastly, both those taking PrEP and those in the deferred arm were able to take post-exposure prophylaxis (PEP) if they wanted, and PEP use was particularly high in the deferred arm. Five percent in the immediate arm took PEP at least once, while 31% took PEP in the deferred arm at least once.

Sex-based PrEP cuts infections by 86%

By David Evans, Director of Education

A French and Canadian study looking at the use of pre-exposure prophylaxis (PrEP) that is tied to when people actually have sex (rather than daily) found that it reduced new HIV infections among men who have sex with men (MSM) by 86% compared with a placebo. The study, called IPERGAY, was presented February 24 at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle.

IPERGAY involves a new intermittent dosing strategy. In the protocol, rather than attempting daily use, participants were asked to take two pills of either Truvada (tenofovir/emtricitabine) or a placebo between 2 and 24 hours before having sex, one pill 24 hours after sex, and another pill 48 hours after sex. If a person continued having sex then they would continue taking two doses after the last sex act. Researchers designed this strategy in hopes that men would be more adherent to the drug compared with daily use and that it would save on costs. Truvada is far, far more expensive than other forms of HIV prevention, such as condoms.

In short, IPERGAY demonstrated that sex-based dosing of Truvada was much more effective than a placebo, that participants appeared to adhere well to the dosing strategy and that the rates of sexually transmitted infections and condomless anal sex did not increase over time. Additional details about effectiveness and incidence, dosing, sexual behavior and side effects are below.

prep Pre-Exposure Prophylaxis News

Efficacy and incidence

In October 2014, IPERGAY researchers announced that the study would be unblinded and that those randomized to the placebo group would be offered Truvada. This was because the difference in the number of new infections was great enough that it would no longer be ethical to maintain the placebo arm. At that time, there were no data offered on the numerical difference between the two arms.

At CROI, researchers reported that the safety review board had halted the placebo arm, because the rate of new infections was so high in those taking a placebo that it was possible to make a firm determination that Truvada was far superior.

In fact, 14 people assigned to take a placebo and 2 people assigned to take Truvada became infected with HIV. This amounted to a rate of new HIV infections per 100 people of 6.75% in the placebo arm compared with 0.94% in those receiving Truvada, a reduction of 86%.

Of note, the two infections in the Truvada arm were found in people who had stopped taking the drug at least one month prior to infection.

Dosing

One of the criticisms of the IPERGAY dosing strategy is that for someone following the regimen and having sex at least once per week or more would be using PrEP similarly to the four times per week that was found to be highly effective in blood level analysis of iPrEx and iPrEx OLE, which were daily dosing studies.

While this remains an open question, and the Centers for Disease Control and Prevention (CDC) has issued a statement warning that only daily use is recommended by the CDC, there were hints in the presentation given this week that intermittent dosing might have merit.

In a presentation at the International AIDS Conference last year in Melbourne, researchers with the IPERGAY study reported that adherence to the IPERGAY regimen was high and that self-report was highly correlated with drug blood levels. This combined with the fact that roughly 20 percent of people in the Truvada arm took PrEP less frequently than once per week could mean that sex-based dosing has merit, at least for some people in some settings. It should be noted, however, that this has only thus far been documented in MSM where condomless receptive anal intercourse is the primary risk behavior.

Sexual behavior

High-risk sexual behavior was common at the start of the study and remained so. The average number of sexual acts in the previous two months among participants at study entry was 10 and this remained essentially unchanged in both the Truvada and placebo arms. Roughly 70% of the participants reported at least one episode of condomless sex in the previous two months and this also stayed the same.

During the study, roughly one third of participants were diagnosed with a sexually transmitted infection. This included 20% with gonorrhea and 10% with syphilis. There were also eight hepatitis C infections over the course of the analysis.

Side effects

Side effects were generally mild and similar to that seen in other PrEP studies. People taking Truvada had higher rates of stomach problems (e.g. diarrhea, stomach pain and nausea) than people taking a placebo. Only one person discontinued Truvada, but this was attributed to a drug-drug interaction.

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HIV Care News

New form of tenofovir TAF looks to be easier on bone and kidney health to the current TDF

By Alan McCord, Director of Education

At the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, two oral sessions presented results on two studies of a new version of tenofovir, tenofovir alafenamide (TAF), vs. the currently used tenofovir disoproxil fumarate (TDF). The first study showed that TAF controls HIV as well as TDF. The second showed less impact on bone and kidney health but possible increases in lipids.

TDF is the most often used drug in HIV regimens today (Atripla, Complera, Stribild, Truvada), but it comes with certain bone and kidney side effects for a small group of people. The hope is for TAF to be a safer though just as effective version of tenofovir for people living with HIV.

TAF differs from TDF in two significant ways: 1) TAF levels in the bloodstream are >90% lower than TDF, and 2) TAF levels within immune cells are >4 times higher than TDF. This means that persistent kidney and bone side effects may be lower for TAF because less of it is found in blood, while the suppression of HIV within cells is perhaps more potent for TAF.

Efficacy results

Results from two Phase III, randomized, double-blind studies (104 and 111) were combined in the first presentation. The studies included 1,733 people who were new to treatment. The two groups were given TAF or TDF along with cobicistat, emtricitabine and elvitegravir ... essentially Stribild with TAF or TDF.

Median age was about 34 and 85% were male, while 56% were white, 25% black and 19% Hispanic. Median viral load was about 38,000 copies (everyone had a viral load \geq 1,000 while 23% were >100,000) and median CD4 count was 427. No one had hepatitis B or C. All had an estimated GFR (eGFR) of 50mL/min or higher. (The eGFR blood test estimates the volume of blood filtered by your kidneys over a given period.)

After 48 weeks of the combined results, the TAF regimen (92% <50 copies) equaled the suppression of the TDF regimen (90%). Very similar results were seen within the individual studies. As for CD4 counts, the TAF regimen increased CD4s on average by 211 cells vs. 181 for TDF. These responses held up despite various starting CD4 counts, viral load levels or age.

The most common side effects in both studies were diarrhea (18%) and nausea (16%). A low rate of serious side effects occurred (8% on TAF, 7% on TDF). Fewer people on TAF stopped the studies (45 on TAF, 71 on TDF). Only about 4% of people developed viral rebound in either study, and of those very few had notable resistance (0.8% on TAF, 0.6% on TDF).

Bone and kidney side effects

In a second presentation of the same two studies, results were presented on TAF's effects on kidney and bone health. The combined results reported on serum creatinine (a blood marker for testing how well kidneys are working), proteinuria (a blood marker for various proteins that also show how well the kidneys are working) and bone density measurements of the hip and spine from DEXA scans.

While no one on TAF stopped the study from any kidney related side effects, four on TDF did. The change in eGFR was -6.6% for TAF vs. -11.2% for TDF (occurring only within the first few weeks). The change in serum creatinine was +0.8 for TAF vs. +0.11 for TDF. The change in proteinuria was -3 for TAF vs. +20 for TDF. No cases of proximal tubulopathy (disease of the kidney's tubules or tissue) occurred in either group.

The average change in lumbar spine bone density was -1.30 for TAF vs. -2.86 for TDF. The average change in total hip bone density was -0.66 for TAF vs. -2.95 for TDF. Not everyone experienced bone loss but more bone loss occurred in those on TDF. A few people also had bone gains (7% on TAF vs. 3% for TDF).

Although changes in bone and kidney health markers favored TAF over 48 weeks, changes in lipids favored TDF. These included LDL ("bad"), HDL ("good") and total cholesterol, and triglycerides. Levels increased slightly in both groups but more significantly in those on TAF. However, the total-to-HDL ratio changed very little in both groups.

The manufacturer of TAF has filed the new combo pill (a modified Stribild of TAF, cobicistat, emtricitabine and elvitegravir) with the FDA. Hopefully we'll hear a decision before the end of 2015.

SOURCES:

D Wohl, et al. *Tenofovir Alafenamide (TAF) in a Single-Tablet Regimen in Initial HIV-1 Therapy*. 2015 CROI.

P Sax, et al. *Renal and Bone Safety of Tenofovir Alafenamide vs Tenofovir Disoproxil Fumarate*. CROI 2015.

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HIV maintenance regimen of cabotegravir and rilpivirine looks promising

By Alan McCord, Director of Education

At the 2015 Conference on Retroviruses and Opportunistic Infections in Seattle, 96-week results were presented from the phase 2b LATTE Study of a new maintenance regimen of cabotegravir and rilpivirine (Edurant). If shown to be effective through its phase 3 study, this approach could offer some people with well controlled HIV the chance to move to just two drugs, and perhaps even move to a periodically injected regimen of those drugs instead of a daily oral dose.

Currently, the NNRTI rilpivirine is FDA approved as oral pills (Edurant, Complera). It's also being studied as a long-acting injectable. The integrase inhibitor cabotegravir (CAB) is currently being studied as both an oral and injectable drug.

LATTE placed 243 people who were new to treatment into one of four groups: CAB 10mg, CAB 30mg, CAB 60mg or efavirenz (Sustiva). They all also took either emtricitabine /tenofovir (Truvada) or abacavir/lamivudine (Epzicom) for 24 weeks. Then, everyone on CAB moved to the maintenance regimen of cabotegravir/rilpivirine (CAB/RPV) through 96 weeks while those on efavirenz continued on their three drugs.

At study start, median CD4 count was 415, and everyone had a viral load above 1,000 (14% above 100,000). Nearly everyone was male and 38% were people of color.

At week 24, 86% of those on CAB had viral loads below 50 copies. By week 96, 76% of those on CAB/RPV (all three groups combined) had undetectable HIV vs. 63% on efavirenz. When looking only at the CAB 60mg group, 84% had undetectable HIV. As for viral rebounds, 4% on CAB (combined) vs. 3% on efavirenz developed detectable HIV after being suppressed.

CD4 counts increased a median of 260 cells for CAB/RPV vs. 290 for efavirenz. Serious side effects were similar between the groups with 14% of those on CAB/RPV experiencing them vs. 19% on efavirenz.

The 30mg dose of this novel maintenance regimen will move on to phase 3 study.

SOURCE:

D Margolis, et al. *Cabotegravir and Rilpivirine As 2-Drug Oral Maintenance Therapy: LATTE W96 Results*. CROI 2015.

Promising results for new HIV attachment inhibitor drug fostemsavir (BMS-663068) as it moves through study

By Alan McCord, Director of Education

At the 2015 Conference on Retroviruses and Opportunistic Infections in Seattle, 48-week results were presented from a phase 2b study of the new attachment inhibitor fostemsavir (BMS-663068). This drug is unique as it targets the surface protein gp120 on the virus which prevents attachment to the CD4 receptor ... something that no other approved HIV drug has done before. Results showed good control of HIV levels and tolerable side effects.

A total of 254 people were assigned to one of four groups with different doses of fostemsavir: 400mg (2x/day), 600mg (1x), 800mg (2x) and 1,200mg (1x). A fifth group took boosted atazanavir (Reyataz). Everyone also took tenofovir TDF (Viread) with raltegravir (Isentress). All had viral loads above 1,000 copies (43% with viral loads >100,000) before starting. Median CD4 count was 230, although 39% started with less than 200 CD4s.

The participants were treatment experienced with many having already had one or more regimens fail. However, they were all still sensitive to all of the study drugs as confirmed by resistance testing. Median age was 39, 60% were men and 30% were white.

Viral loads <50 copies were similar among the 5 groups and reached undetectable levels in 82%, 61%, 69%, 68% and 71% in those on doses of 400, 600, 800 and 1,200mg fostemsavir and atazanavir regimens. CD4 count increases of 140-200 cells were also similar across the five groups. None of these were statistically significant differences.

No serious side effects were reported with fostemsavir, and no one stopped the study because of side effects. No significant abnormalities with blood work were also reported. Fostemsavir has now moved into a Phase III study.

In a presentation from a second study of 42 people, fostemsavir was combined with darunavir, ritonavir and etravirine to tease out possible drug interactions. Those results showed that fostemsavir appears to be well tolerated without significant drug interactions.

SOURCES:

M Thompson, et al. *Attachment Inhibitor Prodrug BMS-663068 in ARV-Experienced Subjects: Week 48 Analysis*.

IS Landry, et al. *HIV-1 Attachment Inhibitor Prodrug BMS-663068: Interactions with DRV/r and/or ETR*. CROI 2015.

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New HIV maturation inhibitor BMS-955176 appears more potent than earlier bevirimat

By Alan McCord, Director of Education

At the 2015 Conference on Retroviruses and Opportunistic Infections in Seattle, results were presented from a phase 2a study of the new maturation inhibitor, BMS-955176. This “second-generation” drug inhibits HIV in the last steps of its life cycle by preventing it from becoming fully mature before it can infect more immune cells.

The significance of this could mean that this new drug class could benefit people whose first and second regimens fail. BMS-955176 also appears to overcome certain HIV gag mutations that the earlier experimental maturation inhibitor called bevirimat could not.

This randomized, 10-day mono-therapy study assigned 48 people new to treatment to one of six groups of these liquid doses of BMS176: 5, 10, 20, 40, 80 and 120mg once a day. Another group of 12 took a placebo. All had viral loads above 5,000 and median CD4 count was about 500. Average age was 37, all were men, and the great majority were white.

Viral loads decreased by more than -1 log over 10 days of treatment, and the effect maxed out with the 40mg dose. The greatest decreases occurred on the 40mg dose at -1.7 logs. When comparing BMS176 to bevirimat, both similarly suppressed wild-type HIV but BMS176 suppressed HIV with gag mutations that bevirimat couldn't in much earlier study.

No serious side effects were seen, and no one stopped the study due to side effects. No serious blood work abnormalities were seen. Diarrhea was the most reported side effect in about 10% of the people on BMS-955176. Phase 2b study will start in early 2015.

SOURCE:

C Hwang, et al. *Antiviral Activity/Safety of a Second-Generation HIV-1 Maturation Inhibitor*. CROI 2015.

BREATHER Study's novel dosing regimen of 5 days on/2 days off controls HIV levels in young people

By Alan McCord, Director of Education

At the 2015 Conference on Retroviruses and Opportunistic Infections in Seattle, results from the 11-country BREATHER Study showed viral control in the great majority of youth who took their regimen for five days but then skipped two. This may offer younger patients a novel way to keep HIV under control while addressing common adherence issues seen in many youth.

However, the study researchers greatly caution against using this short-cycle dosing strategy until more data is collected to confirm that it's safe. These 48-week results apply only to youth on Sustiva-based regimens with well controlled HIV and no viral rebounds before starting the new dosing. Nearly all of the youth will be followed for another 96 weeks.

BREATHER followed 199 youth aged 8-24 years, all of whom took a regimen that included Sustiva (efavirenz). One out of five was 18 or older. Half were randomized to take their regimens daily as they had been doing up to study entry while the other half adopted the novel short-cycle dosing of 5 days on and 2 days off ... essentially the week on with the weekend off.

Everyone who enrolled had already had at least one year of viral loads below 50 copies. None had ever had a viral rebound while on treatment with efavirenz (which greatly reduces the risk for resistant HIV). Everyone had blood work done at 0, 4, 12, 24, 36 and 48 weeks. Just over half were male with median CD4 counts of 793.

After 48 weeks, six on the 5-on/2-off schedule and seven on the daily schedule had developed detectable viral loads >50 copies. When looking at viral loads >400 at week 48, two on the novel dosing and four on daily dosing had viral rebounds. There were no significant differences in lab side effects or inflammation markers between the two groups.

The presentation mentioned that 3 out of 4 of those on the novel schedule said it made their lives a lot easier. They also said their side effects had eased up over the weekends on the new schedule.

Other studies that have looked at weeks or months off treatment (structured treatment interruptions, or STIs) have shown poor results, with increased risks of

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AIDS- and non-AIDS-related conditions. However, the BREATHER Study researchers were clear to state that this was not an STI study. Again, they greatly caution against anyone — youth or older — to attempt this dosing schedule until more long-term follow-up study can ensure this is a safe and effective strategy over time.

SOURCE:

K Butler, et al. *ART With Weekends Off Is Noninferior to Continuous ART in Young People on EFV+2 NRTI*. CROI 2015.

Starting HIV treatment early leads to better health and improved immune systems

By Alan McCord, Director of Education

At the 2015 Conference on Retroviruses and Opportunistic Infections in Seattle, two presentations provided results that describe the benefits to starting HIV treatment “early” in terms of time (within three months of infection) and in terms of CD4 count (>350 cells).

Temprano ANRS 12136 study

A large, 7-year randomized study of 2,056 people from the Ivory Coast assessed the health outcomes of providing HIV treatment immediately or delayed (according to WHO guidelines) and with or without IPT. (IPT, or isoniazid, is often used to treat TB but in this study was used as prevention.) Ivory Coast is a low-income country with high rates of serious bacterial infections such as TB, particularly among people with HIV.

All participants were new to both HIV treatment and IPT and most were women (78%) with a median age of 35. About 40% had CD4s over 500 and all were below 800 cells (median 465). The great majority was followed for more than two years. No one had active TB. All took regimens of emtricitabine/tenofovir (Truvada) with either efavirenz (Sustiva), lopinavir/r (Kaletra) or zidovudine (AZT, Retrovir).

The results showed that immediate HIV treatment and IPT both independently lowered the risk for severe conditions (AIDS diagnosis, severe bacterial infections, non-AIDS cancers, and any-cause death), even when started at CD4 counts above 500. HIV treatment on its own lowered the risk by 44% and IPT on its own lowered it by 35%.

However, throughout the study, WHO guidelines changed a couple of times by increasing the CD4 count at which HIV treatment was recommended. When looking only at those who started at >500 CD4s, IPT’s effect was no longer significant. However, early HIV treatment continued to lower the risk of severe conditions by 44% in this CD4 range.

Royal Free Hospital study

A small retrospective study from London looked at the optimal immune reconstitution of 142 people who had started HIV treatment either within three months of infection (37 people) or during chronic infection but above 350 CD4s (115). Optimal immune reconstitution was defined for this study as a CD4 count >800, CD4 percent at or >40%, and a CD4:CD8 ratio at or >1.

All participants had stayed on continuous treatment for at least 5 years. Median age was about 33 and the great majority were male and men who have sex with men. Median viral loads at study entry were 511,000 for the early starters vs. 278,000 for the late starters.

Results showed that the immune system responses to treatment were excellent in both groups. However, those who started meds earlier showed persistently better outcomes in CD4 counts, CD4 percentage and CD4:CD8 ratios at all 1-, 5- and 10-year time points.

At one year, average CD4 counts were 743 (early) vs. 600 (late), while they were 850 vs. 779 at 5 years, and 966 vs. 874 at 10 years. Average CD4 percentages were 35 vs. 28 at 1 year, 39 vs. 33 at 5 years, and 38 vs. 33 at 10 years. Average CD4:CD8 ratios were 0.95 vs. 0.52 at 1 year, 1.05 vs. 0.78 at 5 years, and 1.09 vs. 0.85 at 10 years.

Of particular note, average time to reaching a CD4:CD8 ratio of more than 1 (a sign of a healthier immune system) was 36 weeks for the early starters vs. 187 weeks for the late starters. Whether this observation results in different health outcomes remains to be determined.

SOURCES:

C Danel, et al. *Early ART and IPT in HIV-Infected African Adults With High CD4 Count (Temprano Trial)*. CROI 2015.

S Kinloch, et al. *Enhanced Immune Reconstitution With Initiation of ART at HIV-1 Seroconversion*. CROI 2015.

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Contraceptive implant levonorgestrel may not be as effective when taking efavirenz (Sustiva)

By Alan McCord, Director of Education

On February 25, an oral presentation at the Conference on Retroviruses and Opportunistic Infections (CROI) 2015 in Seattle showed that women who were using the subdermal implant drug called levonorgestrel (LNG) to prevent pregnancy may not have an adequate level of contraceptive protection due to a drug interaction with the common HIV medication efavirenz (Sustiva). Three out of the 20 women (15%) who had the LNG implant became pregnant.

The implant is popular because it has an extremely low failure rate, and it can be used for up to five years in some women. However, the same protein in the liver that processes LNG also processes efavirenz, so this study sought to find possible drug interactions. Additionally, there has been little prospective research in using subdermal implants with various HIV regimens.

A prospective, non-randomized, open label study in Africa followed 37 women over the course of two years. Seventeen in the first group were not on HIV treatment while the other group included 20 who had started a regimen with efavirenz (Sustiva) at least 30 days before getting the implant. All 20 women had well controlled HIV (<400 copies viral load).

The median age was around 30, and median CD4 count was 568 for the 20 women. However, those on LNG weighed less than the other group. Blood samples were drawn at 1, 4, 12, 24, 36 and 48 weeks to compare the blood levels of levonorgestrel over time while taking a regimen with efavirenz.

Beginning at week 1, the LNG blood levels were 45–57% lower in those on efavirenz compared to the other group, which continued similarly through week 48. By study end, three women on efavirenz had become pregnant while none in the other group did. The study was stopped early given the pregnancy concerns while taking efavirenz.

The study also found that the previously established efficacy level for LNG (180 picograms per mL) may be too low to prevent pregnancy for women who are taking efavirenz. One of the women who became pregnant had an LNG level of 303pg/mL, which was well above that established efficacy level. (A picogram is one trillionth of a gram.)

Given these results (although this was a small study), women who use the LNG implant and are on a regimen with efavirenz or about to start it should be advised about the risks for pregnancy and other forms of contraception.

SOURCE:

K Scarsi, et al. *Levonorgestrel Implant + EFV-Based ART: Unintended Pregnancies and Associated PK Data*. CROI 2015.

The risk for transmission persists through the first six months of HIV treatment

By Alan McCord, Director of Education

At the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, an analysis from the Partners PrEP Study revealed that the risk for HIV transmission within the first six months of starting HIV treatment is still possible before full suppression is attained. Although HIV levels in blood may be undetectable within that time, HIV levels in other bodily fluids — like sexual fluids — may need more time to get to below or near undetectable levels before they're substantially less infectious.

Partners PrEP originally followed nearly 5,000 mixed status heterosexual couples. This analysis included a subset of 496 HIV-negative partners, and assessed those couples every 1 to 3 months for when the HIV-positive partner started treatment (ARVs) and when HIV infection occurred during three time periods: before starting ARVs, during the first 6 months of ARVs, and after the first 6 months of ARVs.

The estimated number of unprotected sex acts (from self-reports) was 8.1% before starting PrEP, 9.9% during the first 6 months, and 10.8% after 6 months. As a result, 3 HIV infections occurred before starting ARVs, 3 infections during the first 6 months of ARVs, and 0 infections after 6 months of ARVs.

A possible reason for the three infections within the first 6 months of HIV treatment could be attributed to HIV levels not being fully suppressed in blood and/or in sexual fluids or tissue. (Sexual fluid/tissue viral loads weren't included in this analysis.) Considering the number of reported unprotected sex acts, these results point to educating couples about various prevention options (such as condoms, PrEP) to further lower the negative

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partner's risk of infection, especially during the first six months of the positive partner being on HIV treatment.

SOURCE:

A Mujugira, et al. *HIV-1 Transmission Risk Persists During the First 6 Months of Antiretroviral Therapy*. CROI 2015.

Using raltegravir or protease inhibitors influences about equal levels of fat gains

By Alan McCord, Director of Education

At the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, the ACTG 5260s study showed increases in body fat after starting a regimen with either raltegravir, boosted darunavir (Prezista) or boosted atazanavir (Reyataz) — with no differences seen between those regimens. Earlier study has linked fat gain to using protease inhibitors while no study has been done on the effect of integrase inhibitors.

The randomized, open-label study assigned 328 people who were new to treatment to one of three groups: a regimen with raltegravir, darunavir or atazanavir — all taken with emtricitabine/tenofovir (Truvada). Median age was 36 while 9 out of 10 were male and nearly half were white. Median CD4 count was 349 and viral load was nearly 35,000. No one had heart disease or diabetes. Blood work for immune inflammation were also taken and compared.

DEXA and CT scans were done at the start and end of the study to measure changes in lean mass, limb fat, subcutaneous abdominal fat (SAT) and trunk and visceral abdominal fat (VAT). After 96 weeks, the median increases in limb fat, SAT, VAT, trunk fat and lean mass (8.2%, 10.9%, 13.9%, 11.4% and 1.3%) were statistically significant across all regimens, although they did not differ significantly between the groups. However, the researchers noted a trend of less fat gain for those who started their regimens at higher CD4 counts.

SOURCE:

G McComsey, et al. *Body Composition Changes After Initiation of Raltegravir or Protease Inhibitors* CROI 2015.

Smoking greatly increases risk for non-AIDS cancers in people with HIV

By Alan McCord, Director of Education

At the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, a new analysis from the NA-ACCORD found that smoking contributes more heavily to the risk for non-AIDS cancers than other modifiable risk factors such as low CD4 count, detectable viral load or AIDS diagnosis. By stopping smoking, people living with HIV could reduce their risk for these cancers by up to 37%. This is significant given the higher rate of smoking seen in people with HIV — about double that of the general population.

The NA-ACCORD looked at 39,554 people who had been diagnosed with a non-AIDS cancer (n=592) from 2000–2009 within their cohort. Cancers with a >6% rate included: anal, breast, Hodgkin lymphoma, liver, lung and prostate. The rates of all other types of cancer (such as colon, oral or skin) were <6%.

The risks for these cancers included being older, history of smoking, low CD4 count, AIDS diagnosis, lipid disorder and hepatitis B or C infection. However, when looking at smoking, it independently raised the risk by 82%. The researchers reported that the risk for these cancers could be reduced by up to 37% by stopping smoking. The risk could be reduced another 8% by keeping CD4s at higher levels and HIV viral load to undetectable levels.

Stop smoking drug, varenicline

While it is vital to understand the significant risk for illness and death attributable to smoking, equally important is determining how to help people to quit, something that is notoriously difficult to do. To that end, French researchers reported 48-week results from using varenicline (Chantix) to help people stop smoking. This ANRS study enrolled 213 regular smokers who were motivated to stop smoking: 102 on varenicline and 111 on placebo. Everyone also received counseling during the first 12 weeks.

At study entry, median age was 45, 83% were male, median lowest-ever CD4 count was 213, and starting CD4 count was 617, while 73% had viral loads <50 copies. Nearly everyone was on HIV treatment. Participants smoked at least 10 cigarettes per day, and had smoked on average about 25 years. Four out of five had tried to stop smoking before.

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At 12 weeks, 34.3% of those on varenicline and 12.6% on placebo had stopped smoking. At 48 weeks, rates fell by almost half as 17.6% and 7.2% were no longer smoking. No changes in CD4 counts or viral loads were noticed. As for side effects, 51% on varenicline vs. 26% on placebo experienced them, while 25% vs. 13% had more serious side effects and 42% vs. 28% experienced psychiatric side effects (sleep problems, depression, hallucinations).

Although varenicline appears to be somewhat safe and effective for people with HIV, successful use of the product occurs in only about 1 out of 5 people over a year's time — comparable to results seen in HIV-negative individuals. For some people living with HIV who want to stop smoking, varenicline may be a good option to try.

SOURCES:

K Althoff, et al. "Smoking Outweighs HIV-Related Risk Factors for Non-AIDS-Defining Cancers". 2015 CROI, Seattle, WA.

C Roussillon, et al. "Varenicline vs Placebo for Smoking Cessation: ANRS 144 Inter-ACTIV Randomized Trial". 2015 CROI, Seattle, WA.

Dutch ATHENA study announces surprising results when using 3TC (lamivudine) over FTC (emtricitabine)

By Alan McCord, Director of Education

At the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, the Dutch ATHENA cohort of HIV-positive people reported that those taking a regimen with 3TC had a higher risk of treatment failure than those taking FTC. However, these results come with some caveats, as detailed in the last paragraph.

3TC (lamivudine, Epivir) and FTC (emtricitabine, Emtriva) have largely been considered interchangeable NRTIs for standard HIV regimens. However, the US Guidelines prefer FTC in first line regimens while 3TC comes in cheaper generic forms for resource-poor communities. There have not been any randomized studies that have compared the two drugs.

To compare the "interchangeability" of 3TC and FTC, ATHENA included 6,031 people new to HIV treatment in this observational analysis. Everyone took 1 of 3 regimens: 3TC or FTC, along with tenofovir (Viread) and ei-

ther efavirenz (Sustiva, n=3,878), nevirapine (Viramune, n=862) or a boosted protease inhibitor (PI, n=1,291).

The results showed that 3TC increased the regimen's failure rate by 2.35 when using efavirenz and by 2.01 when using nevirapine. When using a boosted PI, 3TC increased the risk of failure 1.21 times.

These results, although a little startling, also have their downside. First, this was not a randomized study from which more robust data might be collected. Second, the proportion of people starting FTC was more than six times larger than those on 3TC. Third, many differences more strongly favored FTC such as starting CD4 counts and viral loads as well as percentages of people with hepatitis B or who used injection drugs. Last, these results conflict with several other recently published studies that found no disadvantages to using one of the drugs over the other.

SOURCE:

C Rokx, et al. *Virological Responses to Lamivudine and Emtricitabine in the Nationwide ATHENA Cohort*. CROI 2015.

Financial incentives don't increase case linkage or viral suppression

By David Evans, Director of Education

A large study presented at the 2015 Conference on Retroviruses and Opportunistic Infections in Seattle found that offering gift cards to people to reward them for getting into HIV care after testing positive or for getting their viral loads suppressed doesn't work better than the standard of care. The one exception where financial incentives did seem to work was in smaller clinics, hospital clinics and in people with low virus levels at care entry.

HIV Prevention Trials Network (HPTN) study 065 was designed to determine whether offering financial incentives to HIV-positive individuals would lead to better care outcomes, specifically linkage to HIV care and viral suppression. The instigator for the study was data showing that a significant proportion of those diagnosed with HIV are never linked to care and that an even smaller proportion achieve viral suppression. This has implications both for the health of the person living with HIV, as well as the likelihood that they may pass on HIV to others.

The study randomized 1,346 HIV-positive individuals to receive either financial incentives (FI) or standard of

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care at 34 HIV testing sites and 37 HIV care sites in the Bronx, New York and Washington, DC. The majority were men who have sex with men and most were black or Latino. At testing sites offering FI, people testing positive were given coupons redeemable for \$125 if they had an HIV care visit within three months of testing positive. At care sites offering FI, people could earn \$70 gift cards every three months if their virus was suppressed below 400 copies.

The study found that offering FI to people testing positive did not increase the likelihood that they would have a care visit within three months. Overall, the use of FI did not increase the likelihood that someone would

achieve and maintain viral suppression. There was, however, a benefit to FI for viral suppression in smaller clinics, in hospital-based clinics and in people who had lower viral loads when they entered care.

Finally, FI also increased the odds that a person would remain continuously in care over time in certain situations. These included smaller clinics and in people with higher viral loads at study entry. As well, FI increased care continuity in both hospital- and community-based clinics.

SOURCE:

El-Sadr, et al. *Effect of Financial Incentives on Linkage to Care and Viral Suppression: HPTN 065*. 2015 CROI.

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Hepatitis C Care News

High SVR rates in HIV/HCV co-infected patients with a fixed-dose regimen of ledipasvir/sofosbuvir

By Andrew Reynolds, Hepatitis C Education Manager

The fixed-dose combination of ledipasvir/sofosbuvir (Harvoni) was approved by the FDA in October 2014 for treating HCV in genotype 1 mono-infected persons, but not for the HIV/HCV co-infected. Although some very compelling evidence shows this treatment is effective in co-infected persons — an NIH study of 50 non-cirrhotic co-infected patients had an SVR rate of 98% — the numbers were too small to draw any conclusions regarding its efficacy in larger groups. Results from the ION-4 Study of 335 co-infected patients showed an SVR12 of 96%, offering compelling evidence that co-infected persons can be treated for HCV with a once daily regimen.

ION-4 is a phase 3, multicenter, open label study of co-infected patients with HCV GT1 and 4. The study was open to both HCV treatment naïve and experienced patients, and 20% of participants had compensated cirrhosis. Patients were on various HIV regimens that included emtricitabine and tenofovir disoproxil fumarate plus efavirenz, raltegravir or rilpivirine, and all had HIV RNA <50 copies/mL and CD4 cell count >100 cells/mm³. Of the 335 patients, 276 (82%) were male, 115 (34%) were African American, 56 (17%) were Latino/a, and the average age was 52. The vast majority were GT1 (327, 98%), and

185 (55%) were HCV treatment experienced.

The study results showed high SVR rates, no impact on HIV disease severity or treatment, and minimal side effects. Overall, 321 of 335 patients, or 96%, achieved an SVR12. There were 10 viral relapses and 2 on-treatment failures (both had poor adherence to the regimen), while one person was lost to follow-up and another died of non-treatment related causes (injection drug related fatality). A breakdown of the SVR rates is found below:

Overall SVR	Tx Naïve	Tx Exp	No Cirrhosis	Cirrhosis
96%	95%	97%	96%	94%

All patients maintained stable CD4 counts both during and after treatment, and no patient experienced an HIV virologic rebound. The regimen was very well tolerated, with 257 (77%) reporting some side effects, but all were on the mild to tolerable level. Reported side effects included headaches, fatigue, diarrhea, nausea, arthralgia and upper respiratory tract infections. No one stopped HCV treatment due to these side effects.

Although LDV/SOF has been FDA approved for HIV/HCV co-infection, these results will further support patients and providers who wish to treat HCV off-label. The results of the ION-4 study are very promising for patients with co-infection and show that a once-daily regimen of LDV/SOF can cure people at very high rates with minimal side effects, and no impact on their HIV care.

High SVR12 seen in HIV/HCV co-infected persons on daclatasvir with sofosbuvir

By Andrew Reynolds, Hepatitis C Education Manager

As the direct-acting antiviral era progresses, there are several options for interferon-free treatment for HCV mono-infected persons. While there are some available to HIV/HCV co-infected persons, the need for a safe and effective interferon- and ribavirin-free regimen remains.

The phase 3 ALLY-2 Study, evaluating the effectiveness of daclatasvir (DCV) and sofosbuvir (SOF) for 12 or 8 weeks for patients living with HIV/HCV co-infection, shows very promising results for people with genotypes 1-4 on 12 weeks of therapy.

Daclatasvir is a pan-genotypic (works against GT 1-4) NS5A inhibitor taken once a day. It has been approved for use in Europe, Brazil and Japan, and is under review in the United States. Sofosbuvir, also pan-genotypic, is a NS5B inhibitor taken once a day. Sofosbuvir has already been approved in the United States and Canada. Both drugs are safe and well tolerated, and both have few drug-drug interactions, making them ideally suited for use in people living with HIV.

ALLY-2 comprised 203 patients with HIV/HCV co-infection, with genotypes 1-6. Study participants were given DCV + SOF for 8 or 12 weeks. There were 151 treatment naïve patients who were randomized into the 8 week arm (n=50) or 12 week arm (n=101). There were 52 treatment experienced patients (all of whom took an interferon-based regimen in the past) who were given 12 weeks of treatment. Most (98%) were on HIV treatment, with HIV under control and high CD4 cell counts.

The 8-week results were not promising: 76% of patients achieved an SVR12. The patients who took 12 weeks of DCV + SOF, however, achieved an overall SVR12 of 97%. The breakdown by genotype for the 12 weeks can be found in the following chart:

Patient Type	GT 1a	GT 1b	GT 2	GT 3	GT 4
Tx Naïve	96%	100%	100%	100%	100%
Tx Experienced	97%	100%	100%	100%	100%

The regimen was safe and well-tolerated, and did not impact HIV care and treatment. No one stopped HCV therapy due to side effects or serious adverse events.

With liver disease the leading cause of non-AIDS death and significant morbidity in people co-infected with

HIV/HCV, safe and effective treatments with little drug-drug interaction and impact on HIV disease is extremely important. The combination of DCV + SOF for 12 weeks looks to fit those criteria, and will potentially provide patients and providers with an option to cure HCV without compromising their HIV care.

Adherence to a once-daily medication in hepatitis C mono-infected and HIV/HCV co-infected patients

By Andrew Reynolds, Hepatitis C Education Manager

It is well-established that adherence to HIV treatment is extremely important both to maximize its effectiveness and HIV viral suppression, as well as to prevent the risk of developing drug resistance. As such, people with HIV tend to adhere well to medications as there are many interventions and tools to improve adherence.

Less is known with regards to hepatitis C (HCV) medications and adherence. In a poster presented at CROI 2015 in Seattle, Kerry Townsend and colleagues reviewed the adherence rates of the SYNERGY and ERADICATE studies, and hypothesized that people who were on HIV ARVs would have higher adherence rates to their HCV medications than would HCV mono-infected or co-infected patients not on HIV treatment.

Combined, the two studies had 70 patients, all with genotype 1. SYNERGY was a phase 2, NIAID trial with 20 HCV mono-infected patients taking ledipasvir/sofosbuvir (LDV/SOF) for 12 weeks. ERADICATE was also a phase 2 NIAID trial with 50 people total—13 not on HIV treatment and 37 on treatment—who also took LDV/SOF for 12 weeks. In both studies, adherence was measured three ways: “Medication Event Monitoring System” (MEMS) Caps, pill counts, and patient report.

The following adherence rates were reported:

Patient Group	MEMS	Pill Count	Patient Report
HCV mono-infected	96.7%	98.2%	99.3%
HIV/HCV, No ARVs	97.8%	99.4%	99.8%
HIV/HCV, ARVs	96.6%	97.7%	99.5%

As the chart shows, there were small differences between patient report and MEMS. That said, the adherence rates were high in all groups, regardless of co-infection or HIV

treatment experience. Half (50%) missed no doses, 40% missed 1-4 doses, 3% missed 5-8 doses and 7% missed more than 8.

For all groups, there was a significant drop-off in adherence rates that decreased significantly between week 4 and 12. Although a baseline questionnaire did ask participants about behavioral factors like psychiatric diagnosis, alcohol and substance use, this presentation did not review if any of these factors impacted adherence. Regardless of the adherence to LDV/SOF, 99% (69 of 70) achieved an SVR12.

This small study showed that adherence rates were high across various patient groups, but that for some maintaining consistent adherence over time could be challenging. Although 99% of people achieved an SVR12, the study findings of reduced adherence between weeks 4 and 12 highlight the need for providers and health educators to check in and remind patients to consistently take their HCV medications as prescribed for the full duration of their course of treatment.

The benefits of achieving SVR in HCV mono- and HIV/HCV co-infected persons

By Andrew Reynolds, Hepatitis C Education Manager

Hepatitis C (HCV) infection is a major cause of illness in people living with HIV. HCV-related liver disease is the leading non-AIDS cause of death, and people with HIV/HCV co-infection suffer from higher rates of extra-hepatic complications such as heart disease and bone fractures.

With the advent of new, highly effective direct acting antiviral (DAA) therapies that are equally effective in co-infected persons as they are in mono-infected individuals, a better understanding of the benefits of SVR is needed.

In a poster presentation entitled “The Impact of SVR on Liver Decompensation and Hepatic Fibrosis Markers in HIV/HCV”, Janet Tate and colleagues reviewed data from the Veterans Aging Cohort Study (VACS) and the VA Hepatitis C case registry to evaluate the rates of liver decompensation and death following SVR in mono- and co-infected patients, and to compare changes in fibrosis markers over time in these two groups.

This study looked at 12,067 HCV mono-infected and 372 co-infected patients. All were treated with regimen that included pegylated interferon and ribavirin. In the

mono-infected group, average age was 52, with African Americans representing 21% of the no SVR and 11% of the SVR group. Genotypes 1, 2, and 3 were included, at 82%, 9%, and 9% respectively. In the HIV/HCV co-infection group, average age was also 52, with greater African American representation at 48% in the no SVR and 31% in the SVR group. Genotypes 1, 2, and 3 were included at 82%, 11% and 7% respectively.

To monitor the benefits of SVR over time, the study authors followed the “AST to Platelet Ratio Index” (APRI), a tool to calculate the amount of fibrosis in the liver. The main outcomes for the study were hepatic decompensation, death, platelet count and APRI scores. In this review, the authors concluded that SVR is associated with reducing the risks of decompensation and death in mono-infected patients, and found no decompensation in the co-infected group. Additionally, all patients who achieved an SVR had improvements in their platelet counts and APRI scores, indicating an improvement in their liver fibrosis.

The authors call for future research to compare the decompensation events and fibrosis change after achieving SVR with newer, all-oral DAAs for both mono- and co-infected patients. That said, this study provides exciting evidence for the benefits of treating and curing HCV to reduce deaths and improve the liver function.

Hepatitis C re-infection rates in people after an SVR

By Andrew Reynolds, Hepatitis C Education Manager

A defining characteristic of hepatitis C (HCV) is the fact that a person can get re-infected with the virus if she/he is exposed to it again following cure or spontaneous clearance. Additionally, a person can experience a recurrence, or “relapse”, of the virus following treatment. While this usually happens within 3-6 months from the end of treatment, it rarely occurs later.

It was with this in mind that Andrew Hill and colleagues presented a poster at CROI in Seattle entitled “Five-Year Risk of Late Relapse or Reinfection with Hepatitis C after Sustained Virologic Response: Meta-analysis of 49 Studies in 8534 Patients” (1). This review, which actually looked at 66 studies and 11,071 patients, divided patients into 3 groups: HCV mono-infected persons (“low risk”), HCV mono-infected persons who injected

drugs (PWIDs) or prisoners, and HIV/HCV co-infected persons. All of the patients reviewed were treated with the dual regimen of pegylated interferon and ribavirin. They all were followed for various lengths of time, and HCV recurrence was defined as confirmed HCV RNA following an SVR of at least 6 months.

After combining the various studies, the following results were found:

Patient group	Number	5-yr recurrence	Rate per 100 person yrs
HCV mono-infected, low risk	9,419	1.14%	0.23
HCV mono-infected, high risk	819	13.22%	2.80
HIV/HCV co-infected	833	21.72%	4.78

The chart shows that among low-risk, mono-infected persons, the likelihood of HCV re-infection or recurrence following SVR is very low. People who engage in higher risk activities such as injection drug use or prison (where, one can assume high risk activities such as injection drug use continue to occur in the absence of harm reduction interventions such as syringe exchange or opiate substitution therapy) are at increased risk of re-infection.

Similarly, HIV/HCV co-infected individuals are at greatest risk for re-infection. It has been established that HIV-infected persons are at greater risk of sexual transmission of HCV, and although we don't know the exact risk factors for this group, this study's findings lend support to the need for routine HCV screening for people living with HCV.

Understanding the risk of HCV re-infection is very important in helping shape the argument for providing HCV treatment in PWIDs: they are often excluded from HCV treatment under the argument of 'why treat them when they are only going to get re-infected later'. A 5-year recurrence rate of 13.22% is high, but more information is needed before we can jump to conclusions about PWIDs and HCV re-infection.

An understanding of access to syringe exchange or opiate substitution therapy — two proven interventions that delay and/or reduce risk for HCV infection — would provide us with more context for who and where the re-infection risk was greatest. Although such an analysis is beyond the scope of this poster, further research on this subject is important to help us understand how to best treat and prevent HCV in PWIDs.

HCV re-infection is an important issue in HCV care, treatment and prevention. The authors conclude that the

“large differences in event rates by risk group suggest that re-infection is significantly more common than late relapse”. This can provide a measure of comfort to people who are at low risk for HCV infection following treatment and the achievement of an SVR.

For people at greater risk, however, much work needs to be done. In addition to the further study of the social contexts and risk factors which may facilitate re-infection in PWIDs, people in jail or prison, and HIV/HCV co-infection, we need to increase our efforts at providing them with the tools and health education to stay HCV negative after getting cured of the virus.

HCV risk factors in HIV-infected MSM

By Andrew Reynolds, Hepatitis C Education Manager

Sexual transmission of hepatitis (HCV) is a very important yet poorly understood problem for both providers and patients. Although we have seen a rise in HCV infections in HIV-infected MSM since the early 2000s, there have not been many case-control or cohort studies specifically looking at risk factors and potential modes of transmission in HIV-infected MSM. To that end, Joost Vanhomerig and colleagues from the Netherlands conducted the MOSAIC study, the largest case-control study focusing on transmission of HCV in HIV-infected MSM. Results were presented on a poster at CROI 2015.

Beginning in 2009, HIV-infected MSM with acute HCV across 5 medical centers were given a written questionnaire covering a variety of demographic and risk factors including, but not limited to drug use, sexual risk behavior and other blood-borne risk factors for HCV. To date, there have been 213 MSM included, 82 with and 131 without HCV infection. Performing statistical analysis and comparing the HIV-infected MSM to the HIV-uninfected men as controls, the authors found the following risk factors associated with HCV transmission in HIV-infected MSM:

Sexual Practices Associated with HCV Transmission

- Condomless Receptive Anal Sex
- Ulcerative Sexually Transmitted Infections
- Unprotected (no gloves) Fisting
- Shared Sex Toys

Non-Sexual Factors Associated with HCV Transmission

- Sharing of Straws for Snorting Drugs
- Lower CD4 Cell Counts

In past reviews of sexual transmission of HCV, there are often questions about the role of injection drug use as a potential source of infection in HIV-infected MSM. Only 12 men in this study reported injection histories, and this was not associated with increased risk in this study. Also differing from past results, the study authors did not find a relationship with number of sex partners group sex participation or rectal bleeding. These are still worth considering as potential risk factors going forward. Addi-

tionally the authors call for further research on the role of CD4 count as a potential driver for HCV infection.

The authors conclude that sexual transmission and non-injection drug use are risk factors for HCV infections. This further supports the recommendations that sexually active MSM and those who do not use injection drugs should be routinely screened for HCV as a component of their sexual health and wellness.



HIV Cure News

New “Kick and Kill” HIV cure drug (TLR7 agonist) from Gilead shows promise

By David Evans, Director of Education

A new type of drug, called a toll-like receptor 7 (TLR7) agonist, was able to activate HIV-infected CD4 cells from HIV-positive donors on antiretroviral therapy (ART), leading to the release and replication of virus, according to a presentation at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, WA. Even more exciting, a second study showed that the same drug not only activated cells when given to monkeys infected with the monkey version of HIV, it also lowered the amount of viral DNA within cells. Together, these studies show that the TLR7 agonist is perhaps the most promising drug to come along that could help us “kick” the virus out of cells, so that the body’s immune system can “kill” those infected cells.

Background

Toll-like receptors are receptors on immune system cells that, among other things, can result in the production of proteins that regulate the immune response to viruses, bacteria and other pathogens. In recent years, scientists have begun to characterize the function of these receptors.

TLR7 has been implicated in auto-immune responses (where the body attacks itself), so it is something of a surprise that the TLR7 agonist being studied by Gilead appears to be safe to use. The drug, called GS-9620, is already in Phase II studies as a treatment for hepatitis B, and experience with the drug led scientists at Gilead to believe that it might be effective in a kick-and-kill model aimed at reversing HIV latency.

Study in human cells

Scientists at the Ragon Institute, in Cambridge, MA, took the blood cells of four HIV-positive individuals on ART. Those cells, treated with ART, were incubated for four days with either GS-9620 or a controlled substance (DMO), and were then analyzed for the production of new copies of viral RNA.

The researchers found that HIV RNA levels rose significantly in three of four of the donor cells incubated with GS-9620. Given that the standard HIV treatment strategy is to reduce HIV levels, it might seem counterintuitive that you would want more virus in this case. But increased RNA levels are one sign that the inactive cells harboring the hidden HIV have begun to actively make virus and would thus be more susceptible to being killed.

Study in non-human primates

The second study presented data on 10 monkeys on ART that were infected with simian immunodeficiency virus (SIV), and that were randomized to receive either GS-9620 or a placebo. The GS-9620 was given in an escalating dose every two weeks and then continued at the highest level every two weeks for several more weeks.

Researchers found that SIV RNA levels significantly increased by the third dose and continued to be elevated at later time points. When the scientists looked at SIV DNA levels in multiple tissues they found significant reductions compared with the placebo. An early phase I safety study has been started in HIV-positive humans on ART.

SOURCES:

Sloan, et al. *TLR7 Agonist GS-9620 Activates HIV-1 in PBMCs From HIV-Infected Patients on cART*. 2015 CROI.
Whitney, et al. *Treatment With a TLR7 Agonist Induces Transient Viremia in SIV-Infected ART-Suppressed Monkeys*.