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Reportback from the 2016 Conference on Retroviruses and Opportunistic Infections

In this issue of *PI Perspective*, Project Inform reports on data that was presented at this year's CROI Conference in Boston, MA from February 22–25, 2016.

PrEP

Pre-Exposure Prophylaxis News

Almost-certain case of PrEP failure due to drug resistance reported

by David Evans, Director of Research Advocacy

A case report of a man in Toronto who became infected with a multi-drug-resistant strain of HIV despite apparently very consistent adherence to PrEP was presented at the Conference on Retroviruses and Opportunistic Infection (CROI 2016) conference in Boston today.

Dr David Knox, a doctor at Toronto's Maple Leaf Medical Clinic, said the patient was a 43-year-old gay man who had been on PrEP for two years. At the time he started PrEP he had an HIV-positive partner who was undetectable on antiretroviral therapy, but also had other sex contacts involving the risk of HIV exposure.

He was a regular attender at the clinic and tested for HIV on average every three months. It was suggested to him that he start Truvada PrEP in April 2013 and he appeared to have good adherence to it on the basis of the frequency of pharmacy refills.

Two years later in April 2015 he started having symptoms after a period of exposure to HIV with multiple partners. The symptoms were not classic HIV seroconversion symptoms, and may have had nothing to do with the HIV; they involved an episode of fever with abdominal pain severe enough for him to go for hospital investigation, where a scan revealed an inflamed colon.

During this time he came in for his regular HIV and STI test and this showed he had acute HIV infection, with a negative test for HIV antibodies but a positive test for the HIV p24 antigen, which shows up sooner. His HIV viral load three days later was 28,000 copies/ml —

rather low for acute HIV infection and suggestive that either his PrEP had 'blunted' viral replication without stopping infection, or that the highly drug-resistant virus was replicating weakly.

The patient was adamant that he maintained excellent adherence to PrEP so Dr Knox, by now concerned that he might be seeing a case of genuine PrEP failure, ordered more tests. One was a resistance test, for all antiretroviral drug classes, for his patient's virus, from a sample taken a week after his HIV diagnosis.

The other needs explanation. The patient was treated within a cash-poor public health setting and his old blood samples had not been saved. So there was no way to directly prove that he had drug levels consistent with high adherence around the time of HIV exposure.

There was an indirect way, however. Dr Knox analysed a so-called Dried Blood Spot (DBS) from the patient taken 20 days after he was diagnosed. The point of a DBS test is that it measures drug levels inside red blood cells, rather than inside the white blood cells that HIV infects, or in blood plasma. Drug levels rise much more slowly inside red blood cells, taking 17 days to reach half of their steady-state levels, and a full eight weeks to reach the drug-saturated steady state completely. Drug levels also rise steadily and are less susceptible to short-term peaks and troughs. Drug levels in the patient's DBS were actually 47% higher than the average figure, suggesting consistent PrEP adherence for most of the period covering his exposure to HIV. If he had only been taking the drugs since he learned his diagnosis, the drug levels would only be 47% of the average steady state level or 31% of their actual level in this patient.

This is an indirect way of measuring drug levels. Given that the onset of symptoms occurred four weeks before the patient's HIV diagnosis and the dried blood test was taken over three weeks after, and that the period of risk according to the patient started two weeks before the onset of symptoms, thus leaving nine weeks for the drug to accumulate, this test did not entirely rule out the possibility that he had been off PrEP at the time he took a risk and that this had prompted him to start taking it again. However, the patient insists this is not the case.

There was a small blood sample left over from his diagnostic test, taken three days before the patient learned he had HIV. This revealed high levels of tenofovir and levels of emtricitabine so high they were above the test's limit of quantification. However this was not a test of long-term drug levels and again cannot completely rule out the possibility that he had had a lapse in adherence around the time he was exposed to HIV.

The resistance test showed that the patient had HIV that had no significant resistance to the protease inhibitor class of antiretrovirals. He had one resistance mutation to the first generation NNRTI drug nevirapine, and complete resistance to emtricitabine. He also had extensive resistance to the first-generation NRTI drugs like zidovudine (AZT) and stavudine (d4T), and these mutations also confer some resistance to tenofovir. However he did not have the so-called K65R mutation that confers high-level resistance to tenofovir, and it was estimated that the resistance pattern he did have only confers 1.3-fold resistance to tenofovir, meaning that drug levels 30% higher than those needed for non-resistant virus should have been enough to prevent infection — and he had much higher drug levels than this in the tests. Resistance, however is a complex process and some combinations of mutations can catalyse higher levels of resistance than they would produce alone.

Not relevant to the apparent PrEP failure, but to the spread of drug resistance, was the fact that this patient also had two resistance mutations to the integrase inhibitor drugs and complete resistance to the drug elvitegravir.

Transmission of HIV with integrase inhibitor resistance is very rare, and especially resistance to drugs other than raltegravir, the first integrase inhibitor. The pattern of resistance observed is compatible with the unnamed person who passed on the virus being on a failing regimen of Stribild (the two-class, four-drug combination pill of tenofovir, emtricitabine, elvitegravir and cobicistat). Given that four out of the five first-line HIV drug regimens recommended by the US Department of Health and Human Services are integrase inhibitor-based, and that this drug class is being investigated for use as PrEP, it would be of concern if more integrase inhibitor-resistant virus started to circulate.

The patient himself was put on a potent three-class regimen of dolutegravir, rilpivirine and boosted darunavir and became virally undetectable only three weeks after starting it. The is no0w on a less intensive maintenance therapy.

In conclusion, this is probably not an absolutely clinching case — one would need drug level samples taken at the time of infection for that. But on the balance of probabilities, with three different measures all supporting the

patient's self-report, this is probably the first documented case of the failure ofTruvada PrEP despite high adherence and more-than-adequate drug levels though recently two cases on solo tenofovir were published.

It is not unexpected that there would be occasional cases of PrEP failure; but the fact that this is the first case report among the tens of thousands of people now taking PrEP shows that it is very rare.

SOURCE:
Knox DC et al. "HIV-1 Infection with Multiclass Resistance despite Pre-exposure Prophylaxis (PrEP)". 2016 CROI, Boston, Abstract 169a LB.

Study may guide effective PrEP rollout in young black MSM

by David Evans, Director of Research Advocacy

A study presented as a poster at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, MA reveals that proper support can lead to high acceptance and adherence to pre-exposure prophylaxis (PrEP) among young black men who have sex with men (MSM).

Several demonstration projects have now found that adherence levels to PrEP are lower among black MSM than among their Latino or white counterparts. Moreover, several surveys have also found that awareness and acceptance of PrEP may also be lower among black MSM.

Though experts have presented theories for why this may occur, no studies have been conducted to assess whether interventions tailored to black MSM (the population with the highest rate of new HIV diagnoses in the U.S.) might improve PrEP uptake and adherence in this population who might benefit so much from it.

To explore just that, scientists designed a theory-based counseling intervention to offer and support PrEP use in a culturally competent manner. The HPTN 073 study is researching whether this intervention will lead to PrEP uptake and adherence among black MSM of all ages. The intervention is a client-centered care coordination (C4) that supports PrEP use and adherence, provides linkage and follow-up to address unmet psychosocial needs and provides referrals to practical services. All study participants were also offered PrEP, though they did not have to accept it to participate in the study or receive the intervention.

In all, researchers recruited 226 men. The population was diverse in terms of age, with 40% being below 25 years of age, and geography, the three sites were Los Angeles, CA, Washington, DC and Chapel Hill, NC. Specific risks behaviors and rates of sexually transmitted infections during the study were not included, though having at least a moderate HIV risk was a criterion for inclusion.

The authors report that PrEP uptake and adherence were both relatively high. Seventy-nine percent chose to start PrEP and 68% were still taking it 26 weeks later. Eighty-five percent of PrEP takers reported adherence greater than 50% at week 4 and 78% reported 50% or greater adherence at week 26. Participants could have multiple C4 counseling sessions, and those reporting PrEP use utilized an average of six, while those not taking PrEP utilized an average of four.

There were five infections among those who ever reported taking PrEP, two of whom had stopped taking PrEP quite a while before becoming infected (50 days and 272 days). There were three infections in those not taking PrEP. The rate of new infections was 62% lower among those reporting PrEP use, though the study was not designed to draw a conclusion about effectiveness. Drug blood levels are being collected and analyzed, so true adherence among those who became infected and those who didn't will be known and reported in the future.

Further details from the study are eagerly awaited, and it remains to be determined how well the C4 intervention can be taken up by clinics and organizations where black MSM may be reached, but the results are encouraging.

SOURCE:
D Wheeler, et al. "HPTN 073: PrEP Uptake and Use by Black Men Who Have Sex With Men in 3 US Cities". 2016 CROI, Boston, MA.

Serious kidney problems are rare with PrEP, but increase with older age and better adherence

by David Evans, Director of Research Advocacy

Three presentations at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston offered reassuring news that adverse kidney changes that accompany Truvada use for PrEP are rarely serious and universally reverse after stopping the medication, but also suggested that older people and those with the best adherence might need to be watched more closely.

Tenofovir disoproxil fumarate, one of the key ingredi-

ents in the combination pill Truvada, is known to affect kidney health in people living with HIV, but so is HIV itself. Thus, one of the big questions with the use of Truvada in HIV-negative people is whether kidney problems in PrEP users will be similar, or less frequent and severe, than in people using Truvada for treatment. In randomized controlled studies of PrEP, moderate to severe kidney troubles have been rare and completely reversible, but real world experience and more detailed analyses have been needed. The three presentations at CROI offered deeper insight into kidney health of people on PrEP.

The first presentation, from Monica Ghandi, MD, MPH, analyzed the association of PrEP adherence with the occurrence and severity of reduced kidney function in participants from the iPrEx OLE demonstration project. She reported that when hair samples indicated high adherence, kidney problems — though very rare — were both more likely overall and more likely to be moderate to severe, compared with hair samples indicating poor adherence. In terms of clinically significant kidney function declines, however, age played a huge part. About a quarter of those over 50 had a clinically significant decline, compared with 5% in those under 40, even when the younger cohort had very high adherence.

A similar presentation from Albert Liu, MD, MPH, looked at tenofovir levels in dried blood spots from men who have sex with men and transgender women enrolled in The Demo Project. Once again, higher tenofovir levels and older age were associated with greater reductions in kidney function, but this was also modified by pre-existing kidney health. Less than 2.4% had a decline in a test of kidney function (eGFR) of 10% or more, and drops reversed on cessation of PrEP, but the chance of kidney health declined was much lower in those with good kidney health at the start of the study.

A final presentation, from Kenneth Mygwanya, MB-ChB, MS, looked at the clinical significance of blood and urine measures of kidney function in those taking PrEP in the Partners PrEP study in heterosexual couples in Uganda and Kenya. While reductions in these measures of kidney function are meaningful and sizable reductions are a serious cause of concern, it is not clear how much tests of kidney function are associated with the actual clinical manifestation of the specific type of kidney damage caused by tenofovir, called proximal tubulopathy. What Mygwanya and his colleagues found was that this condition was rarely seen and not meaningfully different between those assigned to the Truvada arm of the study (1.7%) and those assigned to take a placebo (1.3%).

Taken together there are several conclusions and a big question. The first conclusion is that kidney problems are rare and reversible on PrEP. The second is that older people, those with higher adherence and those with poorer kidney function before starting PrEP could be at increased risk of developing clinically meaningful reductions in tests of kidney function. The third is that even when tests indicate a problem, the actual harms might be less than suggested by the tests.

A big remaining question is whether older people and those with moderately reduced kidney function (but not low enough to rule out PrEP) should be monitored more frequently and closely while on PrEP.

SOURCES:

Monica Gandhi, et al. "Higher Cumulative TFV/FTC Levels in PrEP Associated With Decline in Renal Function". CROI 2016, Boston, MA. Abstract 866

Albert Y. Liu, et al. "Changes in Renal Function Associated With TDF/FTC PrEP Use in the US Demo Project". CROI 2016, Boston, MA. Abstract 867.

Kenneth K. Mygwanya, et al. "Rare Incidence of Proximal Tubular Dysfunction With Tenofovir-Based Chemoprophylaxis". CROI 2016, Boston, MA. Abstract 868.

Advances reported in long-acting PrEP

by David Evans, Director of Research Advocacy

A long-acting injectible version of an integrase inhibitor called cabotegravir was found to be safe in humans, according to data presented at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, but the injections were painful for more than half and lasted several days.

The Achilles heal of oral Truvada for PrEP is that daily (or near daily) adherence can be very challenging for some, particularly those most vulnerable to HIV infection: young gay and bisexual men of color, transgender women of color, and young women in high incidence areas of the world. Studies in those populations have found very low rates of adherence. Thus, one of the intriguing possibilities about long-acting formulations of drugs (whether injections, implants or vaginal rings) is the capacity to overcome adherence problems.

To explore the potential of long-acting cabotegravir, researchers enrolled 85 low-risk individuals to receive either the active drug (75 people) or a placebo (10 people). There was a four-week lead-in with oral drug, plus one week off drug, to look for potential side effects before a long-acting injection was given. (That injection of drug will last for weeks and cannot be taken out of the body.) During the injection phase, participants received 800mg (2 injections) into the buttock muscle, 3 three months.

There were no significant differences between cabotegravir and placebo for most side effects, but moderate to severe injection site pain was present in 59% of those on cabotegravir compared with just 5% in those on placebo. The pain also persisted longer in those on cabotegravir.

Drug blood levels were also assessed, and an unexpected finding will affect further studies. The drug was absorbed and eliminated more quickly than anticipated, leading to higher and quicker peaks and lower troughs — this meant that 12 weeks between doses will have to be reduced to 8 weeks. While still an improvement over daily oral dosing for some, it will mean more frequent contact with a health care provider as people will not be able to inject themselves.

One of the weaknesses of long-acting cabotegravir is that low levels of the drug can persist in the blood stream for months after the last dose. If someone disappeared from care or decided to stop PrEP, and became infected with HIV, there is a real chance that the virus would become resistant not only to cabotegravir but also to other integrase inhibitors. The solution to this problem in the next large study will be for someone to switch from injectible to daily oral PrEP, but whether this will prove manageable in real-world settings remains to be seen.

Given all of this, however, it should be noted that when participants were asked at the end of the study whether they would prefer injectible or oral PrEP, 62% preferred injectible.

Other notable data on long-acting PrEP included a very early study of a tenofovir alafenamide implant. An advantage of an implant over an injectible is that it can be taken out, eliminating concerns about irreversible side effects and a long lasting "tail" of low-level drug. In the poster presented at CROI, there is reason to believe that the implant technology results in favorable dispersal of the drug and that it may provide protection for up to one year.

SOURCES:

M Markowitz, et al. "Éclair: Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men." Abstract 106. 2016 CROI, Boston, MA.

E Schesinger, et al. "A Long-Acting Biodegradable Subcutaneous Implant for Tenofovir HIV PrEP." 2016 CROI, Boston, MA. Abstract 879.

hiv HIV Care News

Switching to regimen with new form of tenofovir improves kidney and bone markers

by Alan McCord, Director of Education

At the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, 96-week results were presented from a phase 3 study that switched individuals from a regimen with the older version of tenofovir (tenofovir disoproxil fumarate, TDF) to a newer version (tenofovir alafenamide, TAF) to compare its efficacy and impact on certain health markers, specifically kidney and bone health. These results build upon similar results that were seen with the development of the new single tablet regimen Genvoya that contains TAF, which was approved by the FDA in November 2015. TAF is currently not available as a standalone pill.

As background, most HIV regimens that people take for the first time include two drugs from the NRTI class, or what is called a NRTI backbone. The most prescribed medications for this are Epzicom (abacavir + lamivudine) and Truvada (TDF + emtricitabine [FTC]). These pills — or their components — are listed as recommended and alternative starting regimens in the most recent Federal HIV Treatment Guidelines. So, having less toxic versions of any of these drugs is important to ensuring the ongoing health of people with HIV.

The 1089 Study enrolled 663 people who were taking a regimen that included TDF/FTC and who were virally suppressed <50 copies HIV RNA. At the start of the study, half continued on their current regimens while the other half switched over to the newer form of TAF but with no other changes to their current regimens.

At study entry, everyone had functional kidneys, measured by an eGFR (a marker of kidney health) of 50 mL/min or higher, with the median being 100 mL/mn. Average age was 48 and 85% of the participants were men. About 75% were white and 20% were African American. Average CD4 count was around 640. Of those who switched to a TAF/FTC regimen, 46% were taking a boosted protease inhibitor regimen, 28% were taking an integrase inhibitor and 25% were on some other non-NRTI drug.

As for viral suppression results, 94% of those who took TAF/FTC and 93% of those who continued on TDF/FTC had viral loads <50 copies, showing that TAF/FTC was non-inferior to TDF/FTC.

The rate of serious side effects was exceedingly low, as were discontinuation due to side effects. Those who took TAF/FTC did show better kidney and bone health at 96 weeks. For those on TAF, eGFR improved 8.4 mL/min vs. 2.8 mL/min for those on TDF. The study also followed four other kidney health markers such as urine protein and albumin. All four markers improved for those on TAF while they all worsened for those on TDF.

Bone mineral density was measured at the spine and hip bone at study entry and at 48 weeks. For bone health at the spine, those on TAF showed an average increase of 30% while those on TDF showed a 14% decrease. For bone health at the hip, TAF showed an average increase of 17% while those on TDF showed a 9% decrease.

As for other side effects, rates were similar between the two groups and occurred in up to 10% of the participants. Common side effects included: upper respiratory infections, headaches, nausea, cough, back and joint pain, bronchitis and sinus infection. Similar rates of people in both groups stopped the study due to adverse events (2% for TAF vs. 1% for TDF).

Lab markers showed similar rates in both groups as well. Overall, 21% of those on TAF/FTC had a lab abnormality vs. 19% of those on TDF/FTC. The most significant lab marker changes were various increased cholesterol changes. Although total cholesterol, LDL and triglycerides increased in both groups, those on TAF experienced slightly higher increases. About 4% in each group started a lipid-lowering medication during the 48 weeks.

Other single tablet regimens with TAF are currently approved (Genvoya, Odefsey), in clinical studies (GS9883/FTC/TAF) or under review by the FDA (darunavir/cobicistat/FTC/TAF and TAF/FTC, a newer version of Truvada).

SOURCE:

J Gallant, et al. "Switching to Tenofovir DF to Tenofovir Alafenamide in Virologically Suppressed Adults". 2016 CROI, Boston, MA.

Early results show doravirine regimen as effective as efavirenz regimen

by Alan McCord, Director of Education

At the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, early 48-week results showed that the experimental NNRTI doravirine suppressed HIV levels as well as efavirenz (Sustiva) but with lower rates of side effects. No NNRTIs are currently listed as a "recommended" starting regimen in the federal Guidelines. Efavirenz was recently moved to "alternative" due to its side effects and another "alternative" NNRTI, rilpivirine, should only be used if starting treatment with a viral load <100,000 copies.

This study evaluated viral suppression <200 copies and <40 copies for those who were new to HIV treatment with starting viral loads below and above 100,000 copies. Earlier study in the lab showed that doravirine is effective against common NNRTI-resistant strains.

A total of 216 people were divided into two groups and took either doravirine or efavirenz with tenofovir/emtricitabine (Truvada). Four out of five were white, 93% men, and average age was 36 years. Average CD4 count was about 440. Average viral load was around 40,000 copies with 35% having viral loads >100,000. Both regimens were taken once a day with or without food.

At 48 weeks, no data were given for changes in CD4 counts, but 77.8% of those on doravirine and 78.7% on efavirenz achieved viral loads <40 copies. Also, no data were given on suppression of HIV in those who started with viral loads >100,000 copies.

No one stopped the study due to drug side effects, and severe side effects occurred in 6.5% (doravirine) and 8.3% (efavirenz) of people. Overall drug side events were less common in those who took doravirine (31.5%) compared to those on efavirenz (56.5%). Common side effects included: diarrhea (0.9% doravirine, 6.5% efavirenz),

nausea (7.4%, 5.6%), dizziness (6.5%, 25.9%), headache (2.8%, 5.6%), abnormal dreams (5.6%, 14.8%), insomnia (6.5%, 2.8%), nightmares (5.6%, 8.3%) and sleep disorder (4.6%, 6.5%).

Three people on doravirine and six on efavirenz stopped the study for other reasons.

SOURCE:

GM Gatell, et al, "Doravirine 100mg QD vs Efavirenz +TDF/FTC in ART-Naive HIV+ Patients: Week 48 Results". 2016 CROI, Boston, MA.

New attachment inhibitor shows promise for treatment experienced patients

by Alan McCord, Director of Education

At the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, 96-week results were reported on from a Phase II study of BMS-663068 — a new class of drugs called attachment inhibitors. This type of drug works by attaching itself onto HIV's receptor called gp120, which helps to prevent HIV from attaching to an immune cell to complete its life cycle. BMS-663068 is being studied in people who are treatment experienced and who often have few to no treatment options.

The study enrolled 254 treatment experienced people, defined as having used one or more HIV drugs for at least one or more weeks, with a viral load >1,000 copies. After a 48-week dose-ranging period (the results from which were reported separately), four-fifths of the study participants then took 1,200mg BMS-663068 while the other one-fifth took atazanavir (Reyataz) boosted with ritonavir. Everyone also took tenofovir (Viread) and raltegravir (Isentress), making for a regimen with three drugs from three different classes.

Average CD4 count at study entry was 230 and average viral load was around 65,000 (with 43% of them >100,000 copies). About half had one or more major resistance mutation against protease inhibitors, NRTIs and NNRTIs. Average age was 39, three out of five were male and 62% were non-white.

Just over two-thirds completed 96 weeks of treatment for this analysis. The average CD4 count change was +219 for those on BMS-663068 and +250 for those on atazanavir. As for viral loads, 90% in each group achieved undetectable levels <50 copies. When looking at the viral load threshold of 100,000 copies, 87% of those taking BMS-663068 and 95% on atazanavir reached <50 copies at 96 weeks. For those with starting viral loads >100,000, 94% on BMS-663068 and 80% on atazanavir reached <50 copies.

Clinical-related events occurred less often in the BMS-663068 group (8.5%) compared to the atazanavir group (37%). Jaundice, abdominal pain, headache and nausea occurred more often in the atazanavir group. However, no one stopped the study due to side effects.

Moderate to serious lab abnormalities occurred in <7% of participants which included neutropenia and changes in ALT and AST, creatinine, glucose and uric acid. Abnormal bilirubin levels occurred in 62% of those on atazanavir, a common side effect of this drug.

SOURCE:

E Dejesus, et al, "Attachment Inhibitor Prodrug BMS-663068 in ARV-Experienced Subjects: Week 96 Analysis". 2016 CROI, Boston, MA.

Maintenance regimen of injected cabotegravir + rilpivirine advances

by Alan McCord, Director of Education

At the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, early results from the LATTE-2 study were presented on a maintenance regimen of cabotegravir + rilpivirine given by injection every 4 or 8 weeks. Cabotegravir is an experimental integrase inhibitor while the oral version of rilpivirine is an FDA-approved NNRTI. So far, this 2-drug maintenance regimen appears to suppress viral load as well as other standard 3-drug oral regimens.

HIV drugs have become easier to take over the years — from people taking dozens of pills in the 90s to now often being able to choose from one of six (soon to be seven) daily single tablet regimens. The next step in this evolution is the development of long-acting injectable drugs … very similar to other commonly injected medications like Boniva to prevent osteoporosis. If the LATTE-2 injected regimen works as well as standard oral regimens, then getting an injection once every 30 or 60 days might improve adherence for those who don't mind getting them.

The planned 96-week study enrolled 309 people who had never taken HIV meds. Average CD4 count was 489 and average viral load was around 80,000 (about 1 in 5 had viral loads >100,000). Average age was 35 years and about 4 out of 5 were white. The great majority was men. No one with hepatitis B or reduced kidney function (<50 CrCl) were included.

Everyone started with a regimen of oral cabotegravir and abacavir/lamivudine (Epzicom) for 20 weeks. (This first period of oral cabotegravir allows for immediately stopping the medication if there are side effects, in contrast to the very long presence of the drug in the body from its long-acting form.) At week 20, participants added oral rilpivirine.

Then, only those who had viral loads <50 copies (91%) at end of week 24 moved on. Two-fifths were randomized to switch to a loading dose of long-acting injected cabotagravir and rilpivirine, followed by injected maintenance doses of 400mg cabotegravir LA plus 600mg of rilpivirine every 4 weeks. Another two-fifths received two loading doses, followed by injections every 8 weeks of 600mg cabotegravir LA plus 900mg rilpivirine LA. . Injections were given in the butt muscle. The remaining one-fifth continued on the all-oral regimen

At 32 weeks, 95% of those receiving long-acting injections every 8 weeks and 94% of those injected every 4 weeks had viral loads <50 copies, compared with 91% of those who stayed on the oral regimen. For those who did not respond to any of these regimens, none developed resistance.

Most common side effects for the oral regimen were nausea (9%), indigestion (3%), headache (3%) and fatigue (3%). Reported side effects for the injections were mostly injection site reactions in almost everyone (about 9 out of 10), with 67% reporting pain, 7% swelling and 6% nodules. The great majority of these were mild to moderate in nature, lasting on average about 3 days but sometimes up to a week. They became less common over time but two people stopped the injected regimen because of the reactions.

Other reported side effects from the injections included flu-like symptoms (20%), headache (14%), diarrhea (12%) fever (3%) and fatigue (3%). Nine people stopped the study due to side effects. Lab abnormalities occurred in 16% of those getting the injections and 14% of those on the oral regimen.

SOURCE:

D Margolis, et al. "Cabotegravir+Rilpivirine as Long-Acting Maintenance Therapy: LATTE-2 Week 32 Results". 2016 CROI, Boston, MA

Promising results for new, simpler dosing of raltegravir (Isentress)

by Alan McCord, Director of Education

Although not presented at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, a press release was released near the start of CROI about a phase 3 study of the integrase inhibitor, raltegravir (Isentress). The study, called ONCEMRK, compared a new once-a-day dosing of raltegravir to the current twice-a-day dosing schedule. This simplification could help individuals improve adherence to their regimens which may result in better suppression of HIV over time.

The planned 96-week study enrolled people who hadn't been on HIV treatment before and assigned them to take one of two different regimens: take raltegravir once a day as two 600mg tablets (1,200mg total) or take one 400mg tablet raltegravir twice a day (800mg total), which is the current FDA approved dosing schedule. Everyone also took Truvada (emtricitabine/tenofovir TDF).

Through 48-weeks, the once-a-day dosing showed equal suppression of HIV in both groups. However, specific details of the results — such as percentage of people who were undetectable <50 copies HIV RNA, CD4 count changes and side effects — were not provided in the press release. Detailed findings are expected to be announced later in the year at another conference.

This study differs from another study of raltegravir several years ago that then showed once-a-day dosing did not suppress HIV as well. However, that earlier study only used the 400mg tablet … either one 400mg tablet twice a day or two 400mg tablets once a day: a total of 800mg per day for either dosing schedule. ONCEMRK is now using a higher milligram version of raltegravir at a 600mg dose for a total of 1,200mg per day.

SOURCE:

Press release, "Merck Announces Isentress Phase 3 Met Primary Efficacy Endpoint in HIV-1", February 22, 2016.

Current HPV vaccine does not prevent anal cancer in people with HIV

by Alan McCord, Director of Education

At the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, discouraging news was reported on the HPV (human papilloma virus) vaccine Gardisil, revealing that it failed to reduce the persistence of HPV strains in anal and oral cells. This indicates that it won't protect older people with HIV from developing cervical and anal cancer, something they are at increased risk of compared with their HIV-negative peers.

Currently, Gardisil can be given to younger men and women (11-12 years of age and up to 26 years) before becoming sexually active to help prevent the transmission of the most common strains of HPV that cause genital warts and other conditions that can lead to oral, cervical and anal cancers. It has also been shown to be safe and protective in young people with HIV. The ACTG A5298 study wanted to see if older people with HIV could also benefit from its use.

The study enrolled 575 people who were 27 years of age and older with no previous evidence of cancer due to HPV infection. Any man who entered the study had to report recent receptive anal sex. (This activity has shown to greatly increase the risk and occurrence for HIV-related anal cancer.) Average age was 47, about 4 in 5 were men, 46% were white and 31% were black. Average CD4 count was 602 and 83% had viral loads <50 copies.

The study was planned to screen all participants at the start of the study and every six months over three years. However, it was stopped early due to futility, or it being unlikely that with continued research it could conclusively show the vaccine showed benefit.

At study entry, participants were screened for anal and oral lesions due to HPV infection. Many showed evidence of abnormal anal cells that could lead to cancer: 13–32% had at least one of the four HPV strains (6, 11, 16, 18) covered by the vaccine, while 33% had high-grade lesions (HSIL) and 64% had any grade of abnormal cell conditions. In regards to oral HPV infection, 2–5% had at least one of the four HPV strains. Half got the vaccine while the other half got three placebo injections.

By week 24, 99% of the participants showed antibodies to HPV 16 compared to 48% at study entry, which is a promising result. However, when the study was stopped, data showed there were no significant differences between the two groups for the presence of HPV strains from visit to visit or for persistent anal infection throughout the study.

On the other hand, there was a significant difference between the groups for persistent oral HPV infection. It appears the vaccine reduced the presence of oral HPV conditions for those who got the vaccine. However, given the modest reduction in persistent oral infection, the authors recommend further exploring this effect, though vaccination cannot be recommended in older people. In fact, the authors stress that their results strengthen recommendations for men and women to be vaccinated before exposure to HPV.

The vaccine was safe and well tolerated with mild injection site reactions such as swelling and soreness.

SOURCE:

T Wilkin, et al. "ACTG A5298: A Phase 3 Trial of the Quadrivalent HPV Vaccine in Older HIV+ Adults". 2016 CROI, Boston, MA.