P.I.Perspective

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Reportback from the 2016 International Conference on AIDS

In this issue of *PI Perspective*, Project Inform reports on data that was presented at this year's International Conference on AIDS in Durban, South Africa, from July 18–22, 2016.

tasp Treatment as Prevention

No HIV transmission events from condomless sex between mixed-HIV-status couples

by David Evans, Director of Research Advocacy

The European PARTNER study is now the second large HIV study to determine that full viral suppression due to antiretroviral therapy renders an HIV-positive person nearly completely uninfectious to their HIV-negative sex partners. The study was published in JAMA prior to the AIDS 2016 conference in Durban, South Africa, and was presented at the meeting on July 19, 2016.

Researchers enrolled 888 mixed-status primary couples in 14 European countries — 548 of whom were made up of cisgender heterosexual men and women and 340 who were couples made up of two cisgender men who have sex with men (MSM). Previous vaginal or anal sex without condoms was a study prerequisite. Condomless sex outside of the primary relationship by the HIV-negative partner was reported by 108 MSM and 21 heterosexual men or women. The other primary requirement was that the HIV-positive partner be on fully suppressive antiretroviral therapy.

Despite 22,000 condomless sex acts between MSM partners and 36,000 between heterosexual men and women, there were zero HIV transmissions within the relationships. Ten HIV-negative MSM and 1 heterosexual did become infected from sex with others. Significant genetic differences between the strain of HIV from the positive primary partner and the viral strain in the partner who became infected proved that the transmissions occurred outside the relationships.

While public health and medical experts and HIV advocates heralded the results of the study, all say that hard work remains to update prevention advice to HIV-

positive and HIV-negative people in light of this and the HPTN 052 results, to change laws that criminalize HIV, as well as to further study transmission events in larger populations of MSM and populations not yet studied (such as transgender women and men and people who inject drugs).

SOURCE:
Rodger AJ et al for the PARTNER study group. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA, 2016;316(2):1-11. DOI: 10.1001/jama.2016.5148. (12 July 2016).

prep

Pre-Exposure Prophylaxis

High engagement, maintenance and meaningful PrEP adherence is possible among black MSM

by David Evans, Director of Research Advocacy

While several previous PrEP studies have found higher dropout rates and poorer adherence among black MSM than white MSM in the United States, continuing reports from the first study designed by and for black MSM shows that the right approach can lead to success and that self-reported adherence accurately represents whether these men actually took their medication.

Two investigators from the HIV prevention trials network (HPTN) 073 study presented data from this PrEP demonstration project, which enrolled only black MSM, at AIDS 2016. The first presentation, by Christopher Hucks-Ortiz, described how their culturally tailored model was developed and implemented. Enrolling 226 black MSM at three sites in the United States, the project utilized trained peers for the study staff, who were responsible for recruitment, enrollment and implementation of the support intervention, which offered PrEP to those who wanted it (most did), as well as other risk reduction education and referrals for multiple types of services. As reported at CROI earlier this year (Alan, can you include the link?), most men accepted and stayed on PrEP and study drop out was very low. Hucks-Ortiz commented that having black MSM as the designers and implementers of the study is very likely the reason for its success and something other projects attempting to reach black men should emulate.

The second presentation was by Darrell Wheeler, one of the study's principal investigators. Wheeler reported for the first time on biological tests taken to determine the presence of Truvada in blood, a critical confirmation of adherence. While Wheeler and his colleagues previously reported better self-reported adherence than had been seen among black men in other studies, with an average of 85% reporting 50% or greater adherence throughout the study, and 67% reporting 90% or greater adherence. It's important to remember that four doses per week, which is highly protective. However, it was unknown whether actual adherence matched what people told study staff.

Upon analysis of blood samples, the investigators found that men who reported taking four or more pills per week actually did so. The following factors were associated with high self-reported adherence: being age 25 and older; higher educational attainment, being employed full time, using fewer recreational drugs and having a primary sex partner.

SOURCES:
Hucks-Ortiz C et al. HPTN 073: Successful engagement of black MSM into a culturally relevant clinical trial for PrEP. AIDS 2016 Abstract #WEACO103

Wheeler D et al. Correlates for levels of self-reported PrEP adherence among black men who have sex with men in 3 U.S. cities. AIDS 2016 Abstract #WEACO104.

New analysis finds dapivirine vaginal ring might be highly effective at blocking HIV infection

by David Evans, Director of Research Advocacy

A monthly vaginal ring containing the antiretroviral drug dapivirine might offer a protection rate of up to 92% in women who keep the ring inserted for the full duration of each month.

The ring, which was studied in 2,629 women in the HPTN-020/ASPIRE study, was previously reported to have quite low efficacy in reducing the risk of HIV transmissions, with no difference between women under the age of 21 who received a ring containing the active drug compared with young women who received a ring containing a placebo. The previous presentations, however, were based on self-reported usage of the rings.

A new analysis was presented at AIDS2016 which looked at the remaining levels of dapirivine in each returned ring in a sub-set of the study participants, allowing researchers to calculate with high accuracy how many days a woman actually wore the ring. Based on this, researchers calculated a cut-point level of dapivirine that they categorized as either non-adherent or having a mix of low to high adherence. By that analysis, those with low to high adherence had an HIV risk reduction of 67%. A deeper dive into the data, however, revealed that protection could vary from as high as 75% to 92% in highly adherent women.

SOURCE:

Brown, E et al. Residual dapivirine ring levels indicate higher adhernence to vaginal ring is associated with HIV-1 protection. AIDS 2016 Abstract #TUACO105LB.

Long-acting rilpivirine persists for months in the body

by David Evans, Director of Research Advocacy

A study looking at a long-acting injectible form of the antiretroviral drug rilpivirine revealed that it persists for months after a single dose, most of the time at levels too low to protect against HIV infection, but high enough to cause drug resistance if a person became infected during the period where some drug was present.

The study, reported at AIDS2016, looked at five women and two men who received a single dose of 1,200mg of long-acting rilpivirine. The same long-acting formulation of the drug, in combination with a long-acting form of another drug named cabotegravir, is being tried as HIV treatment in people living with HIV, and cabotegravir alone is being studied for PrEP.

Of the seven people, rilpivirine was detectable in plasma samples of 100% of them at an average of 541 days. The drug was also detectable in endocervical and vaginal fluid, but not in cervical, vaginal or rectal tissue.

It's unclear what the ramifications are for long-acting rilpivirine for PrEP, however, because cabotegravir can persist for up to a year at very low levels, the PrEP study of that drug requires a person to take the oral version for at least 12 months following their last injection of the long-acting formulation. This is to ensure that a person does not become HIV-infected with very low levels of the drug present, a recipe for developing drug resistance.

It would seem that rilpivirine has the same problem. This is less than ideal for people whose reason for a non-oral long-acting version of PrEP is non-adherence, though previous presentations on long-acting cabotegravir indicated that many people would prefer injectible long-acting PrEP to daily oral therapy.

SOURCE:

McGowan I et al. Persistence of rilpivirine following single-dose of long-acting injection. AIDS 2016 Abstract TUACO#103.

Four studies address concerns about PrEP in gay and bisexual men

by David Evans, Director of Research Advocacy

A number of significant concerns were raised even before the battle for PrEP approval in the United States began in 2012. Among the most intense fears about PrEP were the possibility that increases in condomless sex among PrEP users would actually lead to more new infections, that imperfect PrEP use would lead to more drug resistance, and that irreversible toxicity would be common. All of these concerns were addressed in four different presentations at AIDS 2016.

As far as increased HIV risk leading to more infections, the results of the extension phase of the IPERGAY study seemed to put them to rest – at least for now and for most. Among the 400 men who have sex with men (MSM) who enrolled in the original placebo controlled IPERGAY study, 362 participants chose to continue in the study and take Truvada for PrEP. IPERGAY is unique

in that it recommends taking Truvada intermittently around actual sexual activity rather than daily dosing. The researchers found, however, that although condom use declined over time, people who reduced condom use were much more likely to be high users of PrEP. There was only one HIV infection, and that occurred in someone who was not taking Truvada. It should be noted that there was a small subset of people not using PrEP who also reduced condom use, a phenomenon requiring attention.

In regards to resistance, iPrEx principle investigator, Robert Grant, offered an analysis of drug resistance in six randomized clinical trials of PrEP and one demonstration project. While drug resistance did develop in PrEP users, previous publications have illustrated that around one third were due to the failure to detect acute HIV infection before starting PrEP, and almost all of the remainder were due to drug blood levels well below the level needed for protection. Grant's analysis found that when calculating excess risk of developing resistance to either drug components of Truvada over the number of infections averted, the absolute risk was 0.05%.

Lastly, researchers offered a closer look at the impact of Truvada on bone health (in young MSM) and on the kidneys (in a wider range of ages). For MSM between 18 and 22 years of age, Truvada was associated with bone loss. There was a trend toward recovery of bone density over a 48-week follow-up period and a presentation at a previous conference found complete recovery in an older group of males. Further work is needed in younger people, however, and a better way to monitor bone loss and recovery than an expensive DEXA scan.

For kidney health, researchers compared screening every six months (the CDC recommendation) versus every three months. They found that more frequent screening was no more likely to detect a drop in kidney health than would warrant going off PrEP, but even better, the absolute risk for such a drop was less than 1%.

SOURCES:

Sagaon-Teyssier L et al. Reported changes in PrEP and condom use in MSM during the open-label extension of the ANRS IPERGAY Study. AIDS 2016 #WEPEC263.

Grant R et al. Benefits of Pre-exposure prophylaxis relative to drug resistance risk. AIDS 2016 Abstract #TUACO104.

Mulligan K et al. Changes in bone mass after discontinuation of PrEP with tenovofir disoproxil fumarate/emtricitabine (TDF/FTC) in young men who have sex with men (YMSM): Extension Phase results of Adolescent Trials Network (ATN) 110. AIDS 2016 Abstract #WEACO305LB.

Mugwanya K et al. Optimizing the frequency of kidney safety monitoring in HIV-uninfected persons using daily oral tenofovir disoproxil fumarate pre-exposure prophylaxis. AIDS 2016 Abstract #FRAEO106LB.

hiv HIV Care News

Two-drug HIV regimen of dolutegravir and lamivudine controls HIV in a small study

by Alan McCord, Director of Education

Researchers reported that a two-drug combination of ViiV Healthcare's integrase inhibitor dolutegravir (Tivicay) with its NRTI lamivudine (Epivir) produced a sustained reduction in viral loads to less than 50 copies in 18 out of 20 people.

Most regimens contain at least three drugs from two different classes in order to effectively control HIV. However, the small PADDLE study looked at giving just two drugs (dolutegravir, lamivudine) from two classes to 20 people who were new to treatment. If effective, this regimen would reduce a person's long-term exposure to three or more drugs and could possibly reduce costs and perhaps long-term side effects.

Great care was taken to ensure participant safety: average CD4 count was about 500; no one had hepatitis B (which lamivudine alone is insufficient to treat); and all had lower viral loads averaging ~24,000 at screening. Viral load tests were taken very frequently within the first four weeks and nearly monthly afterwards to identify possible early failure.

After 48 weeks, 18 of the 20 people reached viral loads <50 copies, though viral levels greatly decreased within

the first few weeks. One of the remaining two had virus rebound to ~250 copies but then regained control before week 48. No mutations were found. The 20th person died from suicide.

This pilot gives way to additional study that will include people with higher viral loads and lower CD4 counts. ViiV announced two large Phase III studies of this combination to start soon.

SOURCE:

P Cahn, et. al. Dolutegravir-lamivudine as initial therapy in HIV-infected, ARV naive patients: 48 week results of the PADDLE trial. 2016 International AIDS Conference, Durban, South Africa. Abstract FRAB0104LB.

Switching to single pill regimen controls HIV as well as other standard treatment

by Alan McCord, Director of Education

New data show equal control of HIV levels when switching from a standard multi-pill regimen to the single tablet regimen of Triumeq (dolutegravir + abacavir + lamivudine).

The STRIIVING study presented 48-week data on switching to Triumeq from various other regimens in people currently on treatment with controlled viral loads. The Phase 3 study divided 553 people into two groups: the first switched immediately at study start to Triumeq while the other group switched after 24 weeks on their current regimen.

After the first 24 weeks, 85% of the early switch group vs. 88% who stayed on their regimens had undetectable viral loads <400 copies. After 48 weeks, 83% of the early switch group stayed undetectable. In the late switch group, 92% were undetectable after 24 weeks of their switch.

Side effects reported most often were nausea, diarrhea, upper respiratory infection, tiredness and headache. The rate of side effects was 21% within the first 24 weeks of the early switch group and then 22% for their second 24 weeks. The rate was 13% over 24 weeks for the late switch group.

No participant in either group had virologic failure. Ten people in the early switch group stopped the study by week 24 due to side effects, although no one else in that group quit in the second 24 weeks. Four people in the late switch group stopped after their switch.

SOURCE:

JE Lake, et al. STRIIVING: switching to abacavir/dolutegravir/lamivudine fixed dose combination … at week 48. 2016 International AIDS Conference, Durban, South Africa. Abstract. THAB0203.

Long-acting injectable two-drug HIV regimen works well as oral "maintenance" treatment

by Alan McCord, Director of Education

People who switched to a new long-acting two-drug injectable HIV regimen after a lead-in period of oral treatment showed equal control of the virus as those who stayed on the oral regimen.

The LATTE-2 study presented early data that showed that long acting formulations of the experimental drug cabotegravir (CBV) + rilpivirine (RPV, Edurant) — injected either every 4 or 8 weeks — controlled HIV as well as the three-drug oral regimen of CBV + Epzicom (lamivudine + abacavir). This Phase 2b study followed 309 people who were new to treatment.

At week 48, 92% of those getting an injection every 8 weeks, 91% being injected every 4 weeks, and 89% on the daily oral regimen reached undetectable levels. The injections were generally well tolerated (see next article) with very few (2–6%) stopping the study in any group. Injection site reactions were very common but usually mild and 90% resolved within a week with many resolving within a few days. The study will move onto Phase 3 with the injections every four weeks.

SOURCE:

D Margolis, et al. Cabotegravir + rilpivirine as long-acting maintenance therapy: LATTE-2 week 48 results. 2016 International AIDS Conference, Durban, South Africa. Abstract THAB0206LB.

Most study participants were satisfied with a new long-acting injectable HIV regimen

by Alan McCord, Director of Education

A follow-up analysis from LATTE-2 showed that most participants generally favored an injectable HIV regimen to taking daily pills, with many stating that it helped with stigma.

An analysis was presented from 39 in-depth interviews of 27 participants (2 of whom were women) and 12 clinicians of patient experiences with injections. Most rated their satisfaction with getting intramuscular injections every 4 or 8 weeks over at least 32 weeks of treatment as a 5 or 6 on a 6-point scale.

Average age was 37 years and most participants were gay men. Almost all reported some level of side effects with the injected regimen: 82% mild and 17% moderate injection site reactions that included soreness, pain, swelling and nodules usually lasting 1–2 days and at most 7 days. Other side effects included fever, tiredness, headache and rash reported by 4% or fewer people.

Some participants said the injections were simpler and more convenient than daily dosing and helped with their confidentiality. Participants generally preferred the injections to taking daily pills (~80%) and would like to continue on them (~85%). However, some were concerned with the number of clinic visits to get the injections, especially for those injected every 4 weeks.

The 12 clinicians were concerned about the issues that injections may pose in the context of patients missing visits, managing side effects and resistance. More research will be needed to identify who would be good candidates for injected regimens.

SOURCE:

D Kerrigan, et al. Experiences with long-acting injectable ART: … (LATTE-2). 2016 International AIDS Conference, Durban, South Africa. Abstract THAB0204.

Once daily dosing for raltegravir (Isentress) may be coming

by Alan McCord, Director of Education

Early study shows that a higher milligram pill of raltegravir taken once a day controls HIV levels as well as its current twice-a-day dosing.

The ONCEMRK study presented data on 797 people who were new to treatment and who took one of two different doses of raltegravir. The experimental 600mg pill dose taken as two pills once a day (total 1,200mg) together with Truvada suppressed viral load equally to the current twice-a-day dosing of the 400mg pill (total 800mg), with about the same rate of side effects.

Raltegravir is currently dosed as a 400mg pill that's taken twice a day along with other medications to fully suppress HIV. An earlier study found that taking two 400mg pills once a day did not control HIV in as many people as twice daily dosing. Therefore, the new 600mg pill (only slightly larger in size than the 400mg) was developed to explore once-a-day dosing of 1200mg total, rather than the previously attempted 800mg.

After 48 weeks, 88.9% on the once-daily dose vs. 88.1% twice-daily reached viral loads <40 copies. Similar HIV control was seen in those with higher viral loads >100,000.

Both groups in the Phase 3 study showed about the same discontinuation rates due to side effects. What this likely means is that, if approved by the FDA, we may soon see Isentress taken once a day, thereby simplifying treatment. Previous studies in HIV and other diseases has found that the fewer doses per day, the better a person can adhere, usually leading to better control of the virus.

SOURCE:

P Cahn, et. al. Raltegravir (RAL) 1200 mg once daily (QD) is non-inferior to RAL 400 mg twice daily (BID) … week 48 results. 2016 International AIDS Conference, Durban, South Africa. Abstract FRAB0103LB.

Dolutegravir regimen controls HIV better in women than an atazanavir regimen

by Alan McCord, Director of Education

The single tablet regimen Triumeq has been shown to control HIV levels in a greater number of women than a regimen with atazanavir (Reyataz).

The ARIA study in women living with HIV presented data that showed the FDA-approved, single tablet regimen Triumeq (dolutegravir + abacavir + lamivudine) is superior in efficacy and side effects to the regimen of boosted Reyataz (atazanavir + ritonavir) plus Truvada (tenofovir + emtricitabine). These results can provide important information to guide clinicians and patients when making treatment decisions for women.

ARIA followed 495 women who had never been on treatment. Average age was 37 years, average CD4 count

was about 340, and all had a detectable viral load with 28% starting treatment above 100,000 copies. Half took the dolutegravir regimen while the other half took the atazanavir regimen.

After 48 weeks, 82% of those on dolutegravir vs. 71% on atazanavir reached undetectable viral loads <50 copies. (For those above 100,000 copies, 80% on dolutegravir vs. 64% on atazanavir reached undetectable.) Fewer of those on dolutegravir (33%) compared to atazanavir (49%) reported side effects, with the most common being nausea, diarrhea, headache and indigestion in both groups plus jaundice and yellowing of the whites of the eyes in the atazanavir group.

Four percent of women on dolutegravir stopped the regimen vs. 7% on atazanavir. Viral failure occurred in 6% of women taking dolutegravir (none developed drug resistance) compared with 14% taking atazanavir (one of whom did develop drug resistance to emtricitabine that's found in Truvada).

SOURCE:

C Orrell, et. al. Superior efficacy of dolutegravir/abacavir/lamivudine … (ARIA Study). 2016 International Conference on AIDS, abstract THAB0205LB.

Life expectancy for people living with HIV has increased again with recent analysis

by Alan McCord, Director of Education

The Swiss HIV Cohort Study presented additional data this year showing that life expectancy has increased another 34 years for a person who is on HIV treatment and in care.

Data were presented from comparing various life factors that influenced life expectancy in 16,532 HIV-positive people and 1,328,985 people from the general population. The results showed that life expectancy of a 20-year-old who tested positive during the early HAART era (1996–98) had increased from 20.8 years to 54.9 years within the current treatment era (2006–13).

In addition to being on treatment and staying in regular care, a person's level of education also affected these outcomes: higher education increased longevity to 60 years. For those with vocational or compulsory education, life expectancy increased slightly less to 53 years.

Although the same study showed a less robust increase in life expectancy in those who injected drugs or who smoked, the data showed that stopping either of them after testing HIV-positive still added years to a person's life: 5 additional years for those who stopped smoking and 7 more years for those who stopped injecting drugs.

Although this is good news for many living with HIV, there still remain many structural and societal barriers that prevent some individuals from gaining access to regular health care and HIV treatment worldwide. To truly improve the life expectancy of all people living with HIV requires solving barriers such as drug pricing, lack of transportation, poverty, gender inequality and stigma.

SOURCE:

A Guilar, et al. Getting There? Life Expectancy by HIV Status and Education in Switzerland. 2016 International AIDS Conference, Durban, South Africa. Abstract TUPEB031.

hcv

Hepatitis C Care News

HIV/HCV co-infected persons achieve high cure rates with sofosbuvir/velpatasvir: Results from the ASTRAL-5 Study

by Andrew Reynolds, Manager of Heaptitis C Education

The new drug combination of sofosbuvir/velpatasvir, brand name Epclusla, received FDA approval on June 28, 2016 for all HCV genotypes as well for those living with cirrhosis. It was not approved for HIV/HCV co-infected persons, however, as results from the study were not yet available at the time of FDA submission. That said, as the study results of SVR rates of 95% and minimal side effects demonstrate, this combination is a safe and effective option for people living with HIV and HCV.

The ASTRAL-5 study had 106 participants, all co-infected with HIV and HCV and all on HIV treatment. It's worth noting that 30% of the participants had compensated cirrhosis: This is an important group of people to study, as HIV infection speeds up HCV-related liver disease, thus leaving many people with HIV who are also living with cirrhosis.

Of the 106 participants (note: at the time of the study, 2 patients were still waiting for final results), 95% (99/104) achieved an SVR12, or virologic cure. Among those with cirrhosis, the SVR12 rate was 100% (19/19). Of equal importance, treatment experienced patients achieved an SVR12 of 97% (28/29). Existing HCV drug resistance was found in several patients, but it did not impact these high cure rates. There were minimal interactions between HIV and HCV drugs and everyone maintained a stable CD4 count throughout the HCV treatment. Finally, side effects were mild, with headaches and fatigue the most commonly reported. No one stopped their HCV treatment due to side effects.

The ASTRAL-5 Study provides enough evidence to prove that this medication is safe and effective for people living with HIV. Although it is not yet FDA approved for co-infection, patients can take it off-label. This treatment regimen marks another step in an exciting time for HCV treatment in people living with HIV, and we can now begin to envision a world where all people with HIV are cured of HCV and we can make co-infection a thing of the past.