P.I. Perspective

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Reportback from the 2015 International AIDS Society Conference

In this issue of *PI Perspective*, Project Inform reports on data that was presented at this year's IAS Conference in Vancouver, Canada, from July 19–22, 2015.

start

When to Start HIV Medications

START study confirms the benefits of starting HIV treatment at any CD4 count

by Alan McCord, Director of Education

A presentation at the 2015 International AIDS Society conference in Vancouver reported additional results from the START (Strategic Timing of Antiretroviral Treatment) Study that showed significant benefits to starting HIV treatment earlier rather than waiting until later to start: a 57% decrease in combined serious AIDS-related and non-AIDS-related events and death. START was stopped ahead of schedule due to these early positive results. Formal study results were published concurrently in the New England Journal of Medicine.

START began in 2009 in 215 clinics in 35 countries by eventually enrolling 4,685 adults with CD4 counts above 500 who were new to treatment. They were divided into two groups: 1) the immediate start of HIV medications and 2) the delay of treatment until CD4s fell below 350 or the appearance of AIDS symptoms. Participants were followed for a mean of 3.0 years. Regimens included recommended options from the US Treatment Guidelines at the time a person started treatment.

The median viral load at study entry was about 13,000 within a range of about 3,000–43,000. About 1 in 10 had viral loads above 100,000. The median CD4 count overall at study entry was 651, with about a third having 500–600 CD4s, another third with 600–700 CD4s and the final third with >700 CD4s.

About 27% of the participants were women and median age was 36. Racially, 45% were white, 30% were black, 14% were Latino/Hispanic and 8% were Asian. About 1 in 10 was from North America, and about half were men who have sex with men. Pregnant and breastfeeding

women were excluded, although any woman becoming pregnant after study entry stayed in the study.

The results showed, when combined, that there were 42 events of serious AIDS-related or non-AIDS-related events or deaths in the immediate treatment group while 96 events occurred in the delayed group. This resulted in a 57% decreased risk of illness and death for those who started treatment early.

Separating these events out, a total of 14 serious AIDS-related events occurred in immediate treatment vs. 50 in the delayed group. This resulted in a 72% decreased risk of illness. Cases of PCP (1 vs. 5), TB (6 vs. 20), KS (1 vs. 11), lymphoma (3 vs. 10) and other opportunistic infections were the most common events, and they occurred more often for those who deferred treatment.

As for serious non-AIDS-related events, 29 occurred in the immediate treatment group vs. 47 in the other. This resulted in a 39% decreased risk of illness. The most common were non-AIDS cancers (9 vs. 18) and cardiovascular disease (12 vs. 14), although these particular conditions were not statistically significant.

As for deaths, no statistically significant difference occurred between the two groups, given the leading causes of death were due to accidents, suicide or violence.

When looking individually at serious adverse events, hospitalizations and deaths from any cause, bacterial infections occurred more often in those who delayed treatment (14 vs. 36), for a 62% decreased risk. When grouping all events together (295 vs. 355), those who started treatment sooner fared better.

As a result of these data, and data from other studies such as the recent African TEMPRANO study, several Guidelines panels are expected to change their recommendations for treating everyone with HIV. The US Guidelines already recommend this, although just this week they upgraded that to an A1 recommendation: a strong recommendation (A) with one or more randomized studies (1).

SOURCES:

JD Lundgren, et al. *The Strategic Timing of Antiretroviral Treatment (START) Study: Results and Their Implications*. IAS 2015, Vancouver, Canada. July 19–22, 2015.

JD Lundgren, et al. *Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection*. New England Journal of Medicine, July 2015.

cure

HIV Cure-related News

Teenager infected at birth controls HIV for 11 years without drugs

by David Evans, Director of Research Advocacy

An HIV-positive teenager who started antiretroviral (ARV) drugs as an infant and stayed on them for about seven years, is now 18 years old and has been off of all medications for 11 years with very low levels of HIV detected. These results were reported on Sunday, July 19 at the International AIDS Society's Towards a Cure symposium in Vancouver, Canada.

Previous studies have found that when ARV medications are initiated very soon after infection it not only lowers the reservoir of latently infected cells, but also increases by a certain degree the chance that a person can control the virus for some length of time if they stop their medication.

In fact, a French group of 14 adult HIV-positive patients, called the Visconti Cohort, has been described for a couple of years now. These individuals all started ARV medications within three months of HIV infection and stayed on treatment for an average of three years. All interrupted treatment, saw a brief rebound of virus, and then began to control HIV at low levels. This group represented about 10% of a larger cohort of acutely infected people who started and then stopped early treatment. The rest had uncontrolled HIV and had to restart therapy.

In this case, the first pediatric case described, the teen's mother had detectable virus in the last trimester of pregnancy so the teen received three doses of AZT after delivery, but had an increasing viral load. At that point, she was given a cocktail of four drugs and maintained an undetectable viral load except for two periods where adherence was poor.

At 6.8 years the family decided to stop therapy, and with the exception of one blip of 515 copies of virus, the teen has maintained HIV levels under 50 copies for over 11 years. CD4 counts have remained stable and though HIV-specific T cell responses are low, the teen still tests positive for HIV antibodies.

It remains to be seen with these "post-treatment controllers," as they are called, have the same degree of health benefits as people who have undetectable HIV as a result of ARV therapy. Some of the rare individuals who spontaneously control HIV without drugs during their entire infection do sometimes have disease progression, which so far does not seem to be the case with those on treatment.

The case, however, is encouraging and will undoubtedly add to our understanding of how it might be possible to achieve something approaching long-term ARV-free remission.

SOURCE:

P Frange, et al. *HIV-1 Virological Remission for More than 11 Years After Interruption of Early Initiated Antiretroviral Therapy in a Perinatally-Infected Child*. IAS 2015, Vancouver, Canada. July 19-22, 2015.

tasp Treatment as Prevention (TasP)

No HIV transmissions with suppressed virus

by David Evans, Director of Research Advocacy

A landmark study, which proved that treating an HIV-positive person with antiretrovirals reduced their risk of passing on HIV to their sex partners, reported final data at the 2015 International AIDS Society conference in Vancouver, finding no HIV transmissions in mixed HIV status heterosexual couples when the positive partner's virus was fully suppressed.

Study HPTN 052 rocked the world of HIV when it revealed in 2011 that HIV treatment could reduce transmission among heterosexual mixed status couples by 96% or more. This impressive result caused the study's monitoring board to recommend that all HIV-positive individuals in the study be offered immediate antiretroviral therapy rather than having half of them continue to wait until their CD4 count fell below 250 as originally planned.

Researches reported in Vancouver the final conclusions through May 2015 from this international study, which originally enrolled 1,763 heterosexual mixed status couples in 13 countries. By the end of the study, 98% of the HIV-positive partners started treatment, but sufficient numbers in the delayed arm remained off of therapy to reach additional conclusions beyond the 2011 report.

There were 78 new HIV infections among the HIV-negative partners. Researchers compared a segment of the genes of the virus in the HIV-positive and HIV-negative partner to determine if it was likely that any infection came from the positive partner rather than an outside partner. This led the researchers to conclude that 46 of the infections were linked between the primary partners, 43 of which occurred in the delayed treatment arm and 3 in the immediate treatment arm. A reduction of 93%.

When the researchers looked at the 8 linked infections in the immediate treatment arm throughout the entire course of the study, however, none occurred when the HIV-positive partner was suspected to have fully suppressed virus.

prep **Pre-Exposure Prophylaxis News**

New PrEP & women studies: High adherence and effectiveness, but caution for providers

by David Evans, Director of Research Advocacy

Two studies presented at the 8th International AIDS Society in Vancouver Canada (July 19 to 23) offer critical insights about PrEP and cisgender heterosexual women. One found very high rates of adherence and no infections among women taking daily PrEP in an open label fashion, while the other measured adherence and acceptance of three dosing strategies, of which a qualitative analysis suggests that common education and adherence programs may actually worsen suspicion about PrEP and lower adherence.

TDF2 OLE

In the first study, an open label continuation of the Centers for Disease Control and Prevention (CDC) funded TDF2 trial, the CDC's Faith Henderson presented an analysis of adherence among 229 heterosexual cisgender men and women who rolled over from the larger TDF2 efficacy trial (where half were randomized to receive Truvada and half did not). Individuals in TDF2 were asked if they would like to receive 48 weeks of Truvada and be followed regularly. Those who agreed, 229 in all, were tested regularly for HIV and had their adherence measured by both self report and blood level testing for the presence of tenofovir.

Forty-five percent of the participants were female and roughly 70% were single. When looking at self-reported adherence, roughly 90% reported having good or excellent adherence and this held up through the course of the study. Blood level testing in 120 of the 229 revealed that self-reported adherence was highly correlated with having detectable tenofovir in blood. While this is encouraging, and women were validated to have very high adherence, female sex was associated with slightly lower adherence levels.

Overall, the number of sex partners decreased by 12% and the number of condomless sex acts decreased by 39% during the course of the study.

There were no HIV transmissions, though statistics from the earlier TDF2 efficacy trial would have predicted 5 or 6, backing up the finding that Truvada can work well in HIV-negative women.

HPTN 067 (ADAPT)

HPTN 067 is not an efficacy study. Rather, it is designed to measure the coverage of sex acts, acceptability and adherence involved in three Truvada dosing strategies: daily, time-driven (two doses per week not driven by sex) and event-driven, where one dose is taking within 24 hours before sex and another dose 2 hours after.

There are three separate branches of ADAPT, two in men who have sex with men (MSM) and transgender women in either Harlem or Bangkok, and one in heterosexual cisgender women in South Africa. This article focuses on the study in South Africa.

As Dr. Robert Grant from the University of California San Francisco (UCSF) reported, 179 women were randomized 1:1:1 to the three dosing strategies. HIV incidence was high, with 6.8% not enrolled due to being HIV+ at enrollment, indicating that the study was being properly deployed in groups of women at particularly high risk for HIV infection. The median age was 26, 80% were never married and 83% were unemployed.

Based on a device that electronically measured doses dispensed and self-report through weekly phone calls, overall adherence was much better with daily dosing than the other two intermittent dosing strategies, with 75% having good coverage if they were assigned to take Truvada daily, compared with 56% assigned to time-driven dosing and 52% with sex-driven dosing.

To determine the barriers and facilitators to drug taking, Rivet Amico from the University of Michigan, worked with researchers and community to conduct focus groups and interviews with 60 of the women in the study.

Amico explained that through two types of psychosocial analyses it was possible to identify perceptions and values that affected adherence. On one end of the spectrum, among women with the least adherence, Amico found high levels of distrust: about the drug, about the research process and about the medical establishment. On the other end of the spectrum, she defined the group of high adherers as having "mutuality," whereby a participant felt there could be a high degree of benefit both to herself and to her community by participating in the research study. In between were those who felt uncertain

about the drug and the study, and those who wished to be in alignment with the study's aims, but who nonetheless struggled with adherence.

One conclusion that Amico and her team drew from the qualitative work, was that adherence to clinical care and medication taking could be well supported through traditional means. These could include reminder calls and texts and validated adherence support programs support women in keeping their appointments and taking their medications.

Conversely, and quite important, utilizing these measures, which often assume that a woman's wishes about PrEP are in concordance with the researcher or doctor, could push women to report that they are more adherent than they actually are. It is likely, for women who feel more distrust and uncertainty, that other types of interventions will be needed, both for research studies and for programs designed to combine behavioral and biomedical prevention strategies.

SOURCE:

R Grant, et al. HPTN 067/ADAPT Methods and Results from Women in Cape Town. IAS 2015, Vancouver, Canada. July 19–22, 2015.

Daily dosing and text message reminders associated with PrEP adherence in gay men

By David Evans, Director of Education

Two studies presented at the 8th International AIDS Society conference in Vancouver, Canada offered a look at factors associated with adherence to PrEP in men who have sex with men (MSM). In an oral presentation, researchers with the HPTN 067 (ADAPT) study reported on three groups of HIV-negative individuals who were assigned to take Truvada PrEP on a daily, time driven (two times per week) or sex driven (one pill before and one pill after sex) basis and found that daily did better. A second study of a specialized text message adherence support was presented as a poster and found that participant responses to the text system were strongly correlated with blood levels of tenofovir, thus suggesting that text-based systems might help with adherence.

Daily versus intermittent dosing

In the ADAPT study, MSM and transgender women were randomized to the three dosing arms described above in either Bangkok or Harlem in New York City, with 180 men in each city. A separate analysis of ADAPT in 180 heterosexual cisgender heterosexual women is reported here. As there were only four transgender women in the Bangkok and Harlem sites combined it isn't possible to draw conclusions on this particular population.

In the Harlem site, background HIV incidence was incredibly high, with 12% already being HIV-positive at screening. The group enrolled was also quite young and diverse, with roughly one third under the age of 25 and 70% being black and 25% Latino. The Bangkok site also had a relatively high incidence (6%) and enrolled almost all Asian men, who were on average 31 years old and highly educated.

Adherence was measured by an electronic monitoring device and weekly calls. In those reporting sex in the last seven days, blood levels of tenofovir were also measured at 10 weeks after randomized dosing occurred and also if someone seroconverted.

In both cities adherence was better with daily dosing than with time or sex driven dosing, though the difference was greater in Harlem. In Harlem, adherence was 65% with daily, 46% with time-driven and 41% with sex driven. In Bangkok, the rates were 85%, 79% and 65% respectively. One reason given in the qualitative analysis for challenges with adherence with the sex driven dosing is that the post-sex dose needed to be taken two hours after sex. This proved quite challenging for people who wanted to hide their pill from a sex partner or who would literally fall asleep before the time to take the pill arrived.

Though previously researchers had hoped that intermittent dosing might reduce the risk of side effects, neither the time or sex driven dosing arms had reduced rates of side effects compared with daily dosing. Thus, at least in this study, time and event driven dosing appeared less appealing than daily dosing.

Text messaging reminders

A second study, funded by the California HIV Research Program (CHRP) and conducted in Southern California, analyzed data from 152 HIV-negative men MSM taking open label Truvada who received text messages through a system named individualized Texting for Adherence Building (iTAB). The iTAB system sent individualized messages to the participants and asked them to respond whether they took their most recent doses of Truvada.

People who reported "perfect" dosing were combined with those reporting "high" and compared with those reporting "moderate" dosing, and all were compared with

actual tenofovir-disphosphate levels in dried blood spots (DBS), which allowed for analysis of dosing.

There was strong concordance between reported dosing and DBS. Participants with sufficient tenofovir in blood to indicate five or more doses per week were significantly more likely to report that they had taken their medication regularly. Factors associated with poorer adherence included Hispanic ethnicity, younger age and more drug use.

This study shows the utility of an individualized text message support system that could allow for enhanced adherence supports in those who report missed doses.

HIV Care News

New NNRTI doravirine as effective as efavirenz in people new to HIV treatment in early study

by Alan McCord, Director of Education

An oral presentation at the 2015 International AIDS Society conference in Vancouver this week reported 24-week results comparing the new NNRTI doravirine to efavirenz. Both drugs were combined with emtricitabine/tenofovir (Truvada).

The new NNRTI doravirine may offer benefits compared with the other approved NNRTIs, rilpivirine (Edurant, Complera) and efavirenz (Sustiva, Atripla), neither of which are recommended as first line treatment in the US. Efavirenz tends to have neurological side effects for some people while rilpivirine is only recommended for people starting treatment with viral loads <100,000 and CD4 counts >200 cells.

A total of 108 people enrolled in each group: doravirine + Truvada or efavirenz + Truvada. All were new to treatment. The great majority (>90%) who enrolled were men, average age was 35, and nearly 80% were white. A little over 35% had viral loads >100,000 and median CD4 counts ranged from 402 to 430. Less than 10% had 100–200 CD4s cells.

After 24 weeks, 88.9% on doravirine and 87.0% on efavirenz reached a viral load <200 copies. As for viral loads <40 copies, 73.1% on doravirine and 72.2% on efavirenz reached this level. The mean increase in CD4 counts was +154 cells for doravirine and +146 cells for efavirenz.

The rate of experiencing any adverse event was similar between the groups (75.9% on doravirine, 84.3% on efavirenz), although more serious adverse events occurred in the efavirenz group (0.9% vs. 4.6%). Higher rates of diarrhea, dizziness, abnormal dreams, nightmares and sleep disorders occurred with efavirenz.

As for lab abnormalities, doravirine appears less likely to increase LDL cholesterol (1.0% vs. 12.6%) and total cholesterol (3.8% vs. 17.3%). However, bilirubin levels were slightly higher in those on doravirine (3.7% vs. 0.9%).

Of those who stopped the study, 5% came from the doravirine group while 12% came from the efavirenz group.

So far, it appears doravirine suppresses HIV at high levels equal to efavirenz. If it continues to do well in study, we may see doravirine come to market within several years.

Read our earlier coverage of doravirine here: *www.projectinform.org/hiv-news/new-hiv-drug-doravirine-as-potent-as-efavirenz-but-with-fewer-side-effects/*.

SOURCE:

JM Gatell, et. al. *Efficacy and Safety of Doravirine 100mg QD vs Efavirenz 600mg QD with TDF/FTC in ART-Naive HIV-Infected Patients: Week 24 Results*. IAS 2015, Vancouver, Canada. July 19–22, 2015.

New maturation inhibitor BMS 176 shows potent control of HIV in small study

by Alan McCord, Director of Education

An oral presentation at the 2015 International AIDS Conference in Vancouver this week reported promising results from an early 28-day, Phase IIa study of a new maturation inhibitor called BMS-955176. Maturation inhibitors act at the last step of the HIV life cycle and keep the Gag protein from helping the virus to mature and become infectious. No other drugs of this type have yet made it to market.

HIV Care News

During earlier clinical study several years ago, the maturation inhibitor bevirimat was vulnerable to pre-existing genetic mutations in some strains of the virus, with 30% or more of people who took the drug not responding. Development was stopped, and Bristol-Myers Squibb began engineering a new maturation inhibitor not vulnerable to these mutations. An earlier reported, 10-day mono-therapy study of BMS 176 resulted in profound drops in HIV levels, even in people who had the mutations that caused bevirimat to be ineffective.

In the current study, 28 people were divided into 4 groups: 4 took a standard regimen of tenofovir/emtricitabine (Truvada) + ritonavir-boosted atazanavir (ATZ, Reyataz), while another 32 were randomized (8 each) to take either 40mg BMS 176 with ritonavir-boosted ATZ, or 40mg or 80mg BMS 176 with unboosted ATZ.

All participants were male, and nearly everyone was white race. Everyone had a viral load >5,000 HIV RNA (median levels ranged 10,000–30,000 over the 4 groups), and everyone had a CD4 count >200 (median counts ranged 427–581 cells over the 4 groups). In this short study phase, participants could either be new to treatment or treatment-experienced.

After 28 days, the median reduction in viral load for the three BMS 176 groups ranged from -1.66 to -2.18 log while it was -2.22 for the Truvada group. The maximum median reduction in viral load was seen in the Truvada group (-2.39) and the 80mg dose BMS 176 group (-2.23 log).

One person in the 80mg dose BMS 176 group had serious adverse events. No one stopped the study due to adverse events or side effects. Lab abnormalities were higher in the boosted ATZ group, including increased bilirubin levels (which can lead to jaundice). The unboosted regimens had lower median change in bilirubin levels.

BMS 176 is currently enrolling a dose-finding Phase IIb study in people new to treatment and will also conduct a Phase IIb study in people who are treatment experienced.

SOURCE:

C Hwang, et al. *Safety Second-Generation HIV-1 Maturation Inhibitor BMS-955176: Antiviral Activity and Safety with Atazanavir +/- Ritonavir*. IAS 2015. July 19–22, 2015.

Maintenance HIV regimen of rilpivirine and boosted darunavir as effective as three-drug treatment in early results

A presentation at the 2015 International AIDS Society conference in Vancouver reported 24-week results comparing a maintenance regimen of rilpivirine (Edurant) + boosted darunavir (Prezista/ritonavir) to a three-drug regimen of a boosted protease inhibitor and two NRTIs. This could offer some people a new treatment option should they experience significant adverse effects or resistance while on NRTIs.

The PROBE study enrolled 60 people who had controlled HIV for more than six months. Everyone was on a boosted protease inhibitor regimen with either Truvada (emtricitabine/tenofovir) or Epzicom (abacavir/lamivudine). Half of them continued on their regimens while the other half switched to the maintenance regimen.

Four out of five participants were men, average age was 48, and 1 out of 5 had had a previous AIDS diagnosis. No one had HIV that was resistant to rilpivirine and no one had current hepatitis B infection. The great majority (83%) had been on regimens with either boosted atazanavir (Reyataz) or boosted darunavir. The median time on HIV meds was 6.2 years, and the median number of regimens that had been used per person was 3. Average CD4 count was 623 and everyone had undetectable viral loads.

At 24 weeks, after being randomized to switch or stay on their previous regimens, no one had to stop therapy for any reason. Everyone who switched to the maintenance regimen continued to have viral load <50 copies, compared to 86.7% in the other group. Those on the maintenance regimen had a slightly higher increase in CD4s (+24 vs. -13) but fewer CD8 cells (-4 vs. +17). As for fasting triglycerides, the maintenance regimen had less of an increase (+10mg/dl vs. +23mg), and the regimen had larger increases in both total (+14mg/dl vs. -0.7mg) and HDL ("good") cholesterol (+0.6mg/dl vs. -4.2mg).

SOURCE:

F Maggiolo, et al. *Switch from PI/rtv + 2 nucleos(t)ides to RPV+DRV/rtv maintains HIV suppression and is well tolerated*. IAS 2015, Vancouver, Canada. July 19–22, 2015.