

IAS 2019 ANTIVIRAL THERAPY UPDATE

By Lynda Dee

The International AIDS Society (IAS) held their 2019 meeting in beautiful Mexico City, from July 21 thru 24, 2019. Mexico City was grand as were the people who were wonderful, so kind and friendly.

HIV antiretroviral therapy (ART) highlights are provided below.

New Drug for Patients Who Are Resistant to Most ART

GSK's Fostemsavir is a prodrug of temsavir and has been shown to have activity against multi-drug resistant HIV. The BRIGHT Study is a Phase 3 registrational trial, which means it was designed to obtain FDA approval for Fostemsavir. The 272 participants enrolled with only one active HIV drug on board were randomized to receive either fostemsavir or placebo for 8 days. All study participants received fostemsavir after the 8 days. After 96 weeks, 60% of these hard to treat participants had HIV RNA of 40 or lower. There were also 99 people enrolled who had no active ART agents. These participants received an open label optimized regimen with fostemsavir. In this most difficult of groups to treat, 37% of these participants had HIV RNA of 40 or lower. Fostemsavir was also well tolerated. The BRIGHT Study demonstrates that Fostemsavir has the potential to have a significant antiviral impact for those who need new HIV treatments the most.

Switch Studies in HIV Suppressed Patients

Biktarvy (BIK) was studied in GS 4030. BIK is a single tablet regimen (STR), which contains three drugs in one pill, including the new Gilead ART drug abbreviated as TAF. TAF which has been shown to have better bone and kidney side effect profiles than Gilead's previous STR staple TDF. This study demonstrated that BIK, a convenient one pill once a day regimen, is a possible switch option for people who are suppressed on Tivicay and two NRTIs, drugs like AZT and its cousins, even if patients have underlying resistance to some NRTIs. BIK was 93% effective against HIV, while the Tivicay containing regimen was 91% effective which means that BIK is not "inferior" to the Tivicay regimen. There were no safety differences in either regimen and no emerging resistance.

The TANGO study showed us that people on suppressive therapy without resistance can be safely switched to Tivicay plus 3TC, which is an NRTI. This means that if a patient without HIV resistance is successfully suppressed on an HIV regimen which usually contains three to four drugs, they may be able to safely switch to the two drug regimen of Tivicay plus ETC which may have less side effects.

ART Studies in Treatment Naive People

ViiV's 48 week Gemini 1 and 2 studies were the basis of FDA Dovata approval in April of 2019. Dovata plus 3TC was compared to Tivacy plus two Gilead NRTI drugs abbreviated as FTC/TDF.

There were 1,433 participants enrolled in Gemini 1 and 2 with no transmitted HIV resistance. HIV copies in participants could not be any higher than 500,000 or above. Non-inferior efficacy

for FDA approval was demonstrated at 50 copies or less of HIV after 48 weeks on the regimens. The FDA label indication includes people with higher than 500,000 copies of HIV even though they were not included in the study. This may present a problem if people with over 500,000 copies of HIV use this two drug regimen as it may not be strong enough to be completely effective against such high levels of HIV.

The 96 week Gemini 1 and 2 follow-up data were presented at the IAS meeting. Tivicay plus FTC/TDF was 89.5% effective against HIV. Tivicay plus 3TC was 86% effective with no emergent resistance in either arm. There were less bone and kidney adverse events that showed in the Tivicay plus 3TC arm which might be attributed to the fact that the comparison arm included TDF which is known to cause bone and kidney side effects.

There has been some indication from studies that reviewed data on integrase inhibitors (InSTIs) like Tivicay that show that InSTIs, especially Tivicay may cause clinically relevant weight gain. There is also some evidence that TAF causes weight gain. The South African ADVANCE Study addressed this issue, comparing weight gain in three different regimens, Tivicay/FTC/TDF, Tivicay/FTC/TAF and Sustiva/FTC/TDF. As a result of this head to head design, researchers could directly compare an InSTI versus a non-InSTI as well as TAF versus TDF. The ADVANCE Study clearly showed that both Tivicay and TAF are associated with weight gain and that the combination of Tivicay plus TAF cause the most weight gain, particularly in women. We still need more studies to determine whether InSTIs as a class cause weight gain or if this is just a Tivicay issue, and whether or not this weight gain is reversible.

New ART Drugs in Development

New drug development sessions are always the most interesting for me. The IAS meeting did not disappoint here.

The combination of long acting (LA) monthly injected cabotegravir (CAB) and rilpivirine (RPV) is the new regimen closest to FDA approval which is expected by the end of December 2019. It should be noted that this LA regimen is administered via intramuscular (IM) injections. LA CAB and RPV data was presented from the ViiV ATLAS1 and FLAIR2 studies. A pooled analysis of both studies demonstrated non-inferiority efficacy by meeting primary and secondary virologic endpoints compared to oral ART at 48 weeks. Injection site reactions (ISRs) were common, but were mainly non-serious Grade 1 and 2 events with few associated study discontinuations. ISRs were also relatively unusual after the first two weeks. For the first time, we will soon be able to offer patients a once monthly ART regimen. But IM injections will need to be administered by healthcare providers and more than customary provider visits will also be required. Nevertheless, LA CAB/RPV will offer a new, well-tolerated LA two drug regimen that provides the same efficacy against HIV as daily oral regimens.

ViiV also reviewed patient satisfaction with the new LA monthly IM injection regimen. There were high rates of treatment satisfaction and preference for LA CAB/RPV injections compared to daily oral ART. ISRs caused only low discontinuation rates. Generally, IM injections were well tolerated, classified as “totally” or “very acceptable” and improved over time, consistent with a reduced number of ISRs after the first few weeks. It should be noted that only people who are not adverse to injections probably enrolled in these studies. Thus, their tolerability to injections may be higher than that of other patients.

Merck's new drug islatravir (MK8591) is also very interesting. Islatravir data was presented at an IAS late breaker. Islatravir has a 10 fold greater potency than other ARTs, with potent activity against NRTI resistant HIV at low doses, a long half life of 120 hours in adults and the potential for flexible once daily or once weekly oral dosing. The DRIVE2 Study is a multi-part dose ranging study that also compared islatravir plus Pifeltro versus Pifeltro/3TC/TDF. There were no early safety signals. Islatravir/Pifeltro maintained HIV RNA levels at 50 or below for 48 weeks, demonstrating that the combination of islatravir plus Pifeltro creates the potential for a potent, simplified long-acting 2 drug regimen with efficacy comparable to 3 drug regimens. Phase 3 of this study will determine the dose and will include an additional 48 weeks of study follow-up.

Gilead's GS-6207 is a first in class HIV capsid inhibitor with a unique resistance profile relative to existing ART that should be active against multi-class HIV resistance. GS-6207 is administered by subcutaneous (subQ) injection. The study results presented at the IAS meeting demonstrated 6207 activity against many strains of HIV resistant virus in many ART classes, and a 1.5 to 2 log decrease in HIV RNA after a single dose after at 10 days with good tolerability. GS-6207 may be another new long-acting option for people who are resistant to all other drugs or intolerant to current ART regimens.

So, the beat goes on. The HIV pipeline is alive and well. Our HIV armamentarium will soon include long-acting drugs administered monthly instead of daily. This is real progress. I remember when people needed to take their drugs three times a day, some with food, some without food, sometimes with hours between drug doses because of drug-drug interactions. We've come a long way, baby! But we still have a long way to go!