

CROI 2018 HIV ANTIVIRAL UPDATE

By Lynda Dee

CROI 2018 marks the 25th anniversary of Conference on Retroviruses and Opportunistic Infections which was held in Boston, Massachusetts from March 4-7, 2018. CROI is the preeminent HIV science conference in the world. For 25 years cutting edge research in many areas of HIV have been the norm. CROI 2018 did not disappoint. The following is an update of antiviral drugs presented at this year's conference.

Biktarvy is a one pill, once a day, single tablet regimen (STR), that is indicated for both naive and treatment experienced patients. Because it was approved by the FDA on February 7, 2018, it was a much covered topic at CROI 2018. Biktarvy is an integrase inhibitor containing combination regimen which contains bictegravir, emtricitabine, tenofovir alafenamide, and is known as B/F/TAF. The important thing to remember is that this new regimen contains an improved integrase inhibitor, bictegravir, which has an excellent resistance profile and does not require boosting to be effective. Drugs used for boosting often cause increased lipids (fat) which may cause life-threatening cardiovascular side effects, such as heart attacks. TAF also replaces TDF which is included in many of Gilead's previous HIV STRs. TAF is proving to have less kidney and bone side effects than TDF containing regimens. Many treatment experienced studies "switch" studies which compared B/F/TAF to other previously approved regimens in specific populations were presented.

Studies included large Phase 3 studies as well as smaller studies in women and adolescents switching from integrase and protease inhibitor containing regimens to B/F/TAF. These studies will be reviewed below.

In three large Phase 3 trials, presented by Jean-Michel Molina, Biktarvy was found to be non-inferior to integrase inhibitor Tivicay containing regimens, including boosted protease inhibitors Reyataz and Prezista. No treatment emergent resistance was observed. Side effects were comparable, including lipid, bone and kidney profiles which were similar throughout the 48 week study.

Interestingly, in a study of women only presented by Cissy Kityo, women switched to Biktarvy from Triumeq, another integrase inhibitor, containing regimen. Biktarvy was non-inferior to Triumeq with no sign of treatment emergent resistance. Only 2% of women had a viral load above 50 after 48 weeks of therapy with no development of resistance. Side effects were comparable through 48 weeks of treatment. Lipid bone, and kidney safety profiles were also similar after 48 weeks.

Another interesting international study to determine the blood levels as well as safety and tolerability of 24 weeks of Biktarvy in 24 adolescents ages 12-18 was also presented. This work is very important because 20% of all HIV infections in the US in 2015 occurred in youth aged 13-24. In this study, Biktarvy provided a high rate of maintained viral load suppression with no observed treatment emergent resistance. It was also well tolerated. Side effects were mild and

moderate for the most part, with only one adverse event (AE) considered related to Biktarvy and one serious AE. There were no deaths, pregnancies or AEs that lead to study discontinuation. Blood levels of Biktarvy as well as safety and tolerability in these adolescents were similar to that of adults in the Phase 3 trials.

Joe Eron presented the results of a large Phase 3 study where participants switched to an STR regimen containing protease inhibitor Prezista boosted by cobisistat, plus emtricitabine (FTC) and TAF (D/C/F/TAF) from boosted protease inhibitors, plus FTC and TDF. Again, TAF is proving to have less kidney and bone side effects than TDF containing regimens. Participants on the TAF containing regimen had high viral load suppression and low cumulative viral load rebound over 48 weeks. Importantly, these results occurred in participants regardless of prior viral failure and previous experience with multiple ARVs. No treatment emergent resistance was observed. The side effects in the TAF arm were also similar to the control arm in overall participants across all subgroups.

In another D/C/F/TAF switch study, age, gender and race analyses were presented. Low rates of non-inferior virologic rebound were described and no treatment emergent resistance developed. Improved bone and kidney safety profiles were also observed regardless of age, gender or race in virologically suppressed participants that switched to D/C/F/TAF. Study results were limited by insufficient enrollment of people older than 50, women and black/African Americans. Limited enrollment of these important populations make definitive statements about bone and kidney safety profiles in these groups impossible.

Randolph Matthews from Merck presented data on multiple doses of oral MK-8591, a nucleoside reverse transcriptase inhibitor (NRTI) which is a very attractive new drug because very small doses of MK-8591 may be able to achieve long-acting dosing intervals for HIV treatment as well as prevention.

It should be noted that ViiV is also developing new long-acting treatments for HIV treatment and prevention, including intramuscular injections of cabotegravir plus Edurant for HIV treatment and intramuscular injections of cabotegravir for HIV prevention. ViiV's long-acting pipeline is further ahead of Merck at this juncture. But MK-8591 may make oral dosing as well as implantable dosing possible instead of requiring injections.

Data presented at CROI found that MK-8591 was generally well tolerated at 5mg for up to 6 weeks. Levels of MK-8591 were above efficacy projected levels after a single dose of .25mg in the blood as well as in a limited analysis of rectal and vaginal tissue levels of MK-8591. This rectal and vaginal data make MK-8591 a potential HIV prevention candidate.

MK-8591 will be studied in a Phase 2 study combining Merck's Pifeltro plus Epivir which has a generic equivalent. The study is active, but is not yet open to enrollment.

CROI's 25th anniversary ARV presentations were very exciting, covering drugs with better safety profiles as well as new long-acting agents which may be dosed orally and as implants. Stay tuned for more exciting new pipeline ARV drugs for HIV treatment and prevention.