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From *TreatmentUpdate 222*

The evolution of integrase inhibitors

The first integrase inhibitor, raltegravir (Isentress), was licensed in Canada and other high-income countries a decade ago. In subsequent years, two other integrase inhibitors were approved:

- dolutegravir (Tivicay), and together with abacavir and 3TC in a pill called Triumeq
- elvitegravir in a pill called Stribild with cobicistat, tenofovir TF and FTC (emtricitabine)
- elvitegravir in a pill called Genvoya with cobicistat, TAF (tenofovir alafenamide) and FTC

In 2017 a new formulation of raltegravir, called Isentress HD, was approved in high-income countries. This formulation is available in Canada and is taken once daily.

Integrase inhibitors have earned a privileged place in many treatment guidelines because of their potency against HIV. When used as part of the initial therapy of HIV, integrase inhibitor regimens usually lower the amount of HIV in the blood (viral load) quickly compared to other regimens.

Regimens containing elvitegravir need a boosting agent called cobicistat. This latter drug raises and maintains the level of elvitegravir in the blood so that once-daily dosing is possible. However, a disadvantage of cobicistat is that it can interact with many other medicines, raising or lowering their levels in the blood, in a manner similar to an older boosting agent, ritonavir.

Probably by mid-2018, a new integrase inhibitor called bictegravir will be approved in Canada. Bictegravir will be co-formulated (put into one pill) with two other anti-HIV drugs—TAF and FTC. This pill can be taken once daily. Unlike elvitegravir-containing regimens, bictegravir will not require boosting.

Later in this issue of *TreatmentUpdate* we will have reports from two pivotal clinical trials about the effectiveness and safety of bictegravir + TAF + FTC when compared to dolutegravir-containing regimens. In general, both regimens were effective and tolerated and had low rates of mental health and sleep issues. Such low rates are normal in randomized clinical trials of anti-HIV drugs. These trials enroll people who are relatively well. After licensure, it is important that large studies be conducted to monitor people in the community who use the approved medicines to assess if rates of side effects are different from those in randomized clinical trials. Real-world studies may also detect rare and, in some cases, long-term side effects that were not seen earlier.

A major drawback of the initial clinical trials for newer integrase inhibitors is that too few women were enrolled. As a result, pharmaceutical companies have been required to conduct studies with HIV-positive women. Such studies have been done with dolutegravir and are underway with bictegravir.

Back to bictegravir

A pill containing bictegravir + TAF + FTC will have the following advantages:

- Prior to initiating therapy, testing for possible hypersensitivity to abacavir will not be required (as it is with abacavir-containing regimens such as Triumeq, which also contains the integrase inhibitor dolutegravir).
- The combination of TAF + FTC will have potent activity against hepatitis B virus, which is useful for people co-infected with this virus.

Commenting on the pivotal bictegravir trials, doctors in London, England, and Johannesburg, South Africa, made the following points:

Rifampin (used in the treatment of tuberculosis)

"Although dolutegravir can be co-administered with the strong [enzyme] inducer rifampin at a doubled dose of 50

mg twice daily, bictegravir dose adjustment data are unavailable and non-co-formulated bictegravir to promote such dose adjustments might not be available."

Pregnancy

"Although there are accumulating data regarding safety in pregnancy for dolutegravir, both bictegravir and TAF need to show safety in pregnant women and their infants."

In treatment-experienced people

The first phase III clinical trials with bictegravir have focused on people new to treatment. However, clinical trials with treatment-experienced HIV-positive people are underway and results from this population will be released over the coming months.

—Sean R. Hosein

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