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From *TreatmentUpdate 222*

Bictegravir vs. dolutegravir

Bictegravir is an emerging integrase inhibitor that is co-formulated (put into one pill) with two other anti-HIV drugs —TAF (tenofovir alafenamide) and FTC.

This co-formulated drug is undergoing clinical trials in people with HIV. The first phase III trials are reported in this issue of *TreatmentUpdate*. In this report we will focus on one of those trials that compared the following regimens:

- bictegravir + TAF + FTC + placebo
- dolutegravir + TAF + FTC + placebo

In this clinical trial, both regimens were highly effective and tolerated over the course of one year. Side effects were less common among bictegravir users (18%) compared to dolutegravir users (26%).

Study details

Researchers in the following countries enrolled more than 600 HIV-positive people for this study:

- Canada
- Australia
- Belgium
- Dominican Republic
- France
- Germany
- Italy
- Spain
- UK
- United States

Researchers analysed data collected from 320 people who received the bictegravir regimen and 325 people who received the dolutegravir regimen.

The average profile of participants upon entering the study was as follows:

- 88% men, 12% women
- 60% of participants were in the U.S.
- nearly 90% of participants had no symptoms of HIV infection
- viral load – 28,000 copies/mL
- 15% of participants had a viral load greater than 100,000 copies/mL
- CD4+ count – 440 cells/mm^3
- hepatitis B virus co-infection – 3%
- hepatitis C virus co-infection – 2%

Results

After one year the results suggested that, overall, both study regimens had similar effects. Here are the proportions of participants on each regimen with a viral load less than 50 copies/mL after one year:

- bictegravir regimen – 89%
- dolutegravir regimen – 93%

This difference was not statistically significant.

When researchers tested blood samples with a viral load assay that had a lower limit of 20 copies/mL, here is the distribution of the proportions of participants with a suppressed viral load:

- bictegravir regimen – 82%
- dolutegravir regimen – 87%

This difference was not statistically significant.

The lower overall levels of virological suppression seen with bictegravir occurred because more participants (a total of 11) who took this drug left the study prematurely for a variety of reasons (such as losing touch with the clinic, moving, withdrawing consent for unspecified reasons, and so on). Among people who were taking the dolutegravir regimen, three people left prematurely for similar reasons. (The virological data from such people are not used in the final analysis of any drug's efficacy.)

The following factors did not affect a person's response to the study regimens:

- age
- race/ethnicity
- viral load
- CD4+ count
- region/country

The fourth week

When used as part of combination therapy (ART), integrase inhibitors can quickly lower viral load in the blood. At the fourth week of the study the proportions of participants with a viral load less than 50 copies/mL were as follows:

- bictegravir regimen – 75%
- dolutegravir regimen – 80%

This difference was not statistically significant.

Changes in CD4+ cell counts

After one year, CD4+ cell counts increased by the following average amounts in participants:

- bictegravir regimen – 180 cells/mm^3
- dolutegravir regimen – 201 cells/mm^3

This difference was not statistically significant.

Adverse events

The term *adverse events* is used to describe a range of unfortunate events that can occur to participants during a clinical trial. Such events may be driven by the underlying disease process, the study drugs or circumstances that have nothing to do with the study (such as accidents).

Adverse events that were bothersome or serious enough to cause people to prematurely leave the study were distributed as follows:

- bictegravir regimen – five people left prematurely
- dolutegravir regimen – one person left prematurely

People who were taking bictegravir prematurely left the study for the following reasons:

- heart stopped beating (cardiac arrest) – one person
- paranoia – one person
- chest pain – one person

- enlarged abdomen – one person
- a combination of sleeping problems, headache, depression and gastrointestinal problems – one person

An investigation concluded that all of these adverse events, except for cardiac arrest and paranoia, were related to the study drugs.

The person who was taking dolutegravir and who left the study prematurely did so because of red, itchy skin. This was not considered related to exposure to the study drugs.

Common side effects

Most side effects reported were generally of mild-to-moderate intensity. Below is the distribution of common side effects:

Headache

- bictegravir regimen – 13%
- dolutegravir regimen – 12%

Diarrhea

- bictegravir regimen – 12%
- dolutegravir regimen – 12%

Nausea

- bictegravir regimen – 8%
- dolutegravir regimen – 9%

Lack of energy

- bictegravir regimen – 6%
- dolutegravir regimen – 8%

Difficulty falling asleep and/or staying asleep

- bictegravir regimen – 5%
- dolutegravir regimen – 4%

Serious symptoms of side effects were rare, occurring in less than 2% of participants on either regimen.

Deaths

Three people died while in the study, distributed as follows:

- bictegravir regimen – one person developed an infected and inflamed appendix and subsequently the infection became overwhelming and his heart stopped beating
- dolutegravir regimen – one death was from an unknown cause and the other from a suspected blood clot in the lung

It seems unlikely that the study medicines caused these deaths.

Pregnancy

Three women on each study regimen became pregnant during the study. In all cases the women's doctors changed their regimens to other combinations. In four cases the women decided to carry the fetus to term and no deformities were found in the infants.

Note that due to the small proportion of women present in this study no firm conclusions about the safety of bictegravir can be drawn (a clinical trial of dolutegravir regimens in women has already been conducted). A clinical trial of a bictegravir regimen is underway among HIV-positive women.

Lab test results

Several abnormal laboratory test results occurred in the following proportions of participants on each regimen:

- bictegravir regimen – 17%
- dolutegravir regimen – 13%

No trend with these abnormal results was seen in participants. However, researchers noted that participants who took bictegravir and who had higher-than-normal levels of liver enzymes (AST, ALT) generally had a number of health issues that affected the liver when they entered the study:

- elevated levels of AST and ALT
- infection with hepatitis A virus
- excessive drinking of alcohol

People who take bictegravir or dolutegravir tend to develop a small but elevated level of the waste product creatinine in their blood. This also occurs if people, regardless of their HIV infection status, take the anti-ulcer medicine cimetidine (Tagamet). The modest elevation of creatinine that occurs during the use of bictegravir or dolutegravir is not considered harmful by researchers and normalizes when these drugs are discontinued.

There were no cases of kidney injury during the study.

No significant changes in levels of cholesterol and triglycerides in the blood were detected.

Bear in mind

1. Regimens that contained bictegravir or dolutegravir were generally well tolerated and symptoms of serious side effects were rare, occurring in less than 2% of participants.
2. Both bictegravir and dolutegravir have powerful anti-HIV activity.
3. The study team stated that a regimen of bictegravir + TAF + FTC in a single pill "could be a simple, effective and well-tolerated initial treatment for HIV."
4. A relatively small proportion of participants had severely weakened immune systems (12%) and/or high viral loads (19%) prior to entering the study. Ten years ago, these proportions probably would have been greater. What changed during the intervening decade is that data increasingly suggested that starting ART earlier in the course of HIV disease results in better health. Also during that period, treatments became easier to tolerate. So the small proportion of people with severely weakened immune systems and/or high viral loads seen in the present study is likely to be reflected in many clinics in high-income countries.

Availability

A single pill containing bictegravir + TAF + FTC will likely first be approved in the U.S. later in 2017 and then by mid-2018 in the European Union and Canada. The manufacturer of these drugs, Gilead Sciences, seems unlikely to make a pill containing bictegravir alone.

—Sean R. Hosein

REFERENCE:

Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lance*t. 2017; *in press* .

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