I ANTI-HIV AGENTS

A. Know your integrase inhibitors

Anti-HIV drugs can be divided into several classes, such as nukes, non-nukes, protease inhibitors, co-receptor blockers and so on. The latest class of medicines for the treatment of HIV is called integrase inhibitors. The following are two commonly used integrase inhibitors:

- raltegravir (Isentress)
- elvitegravir (in Stribild, a pill that also contains cobicistat, tenofovir and FTC)

Integrase inhibitors are generally well tolerated and tend to have fewer side effects than other commonly used HIV medications. Raltegravir in particular has had relatively few interactions with other drugs.

Until recently, integrase inhibitors have had to be taken either twice daily (as is the case with raltegravir) or with a boosting agent (another drug that raises the level of the integrase inhibitor or other drugs). A boosting agent commonly used in HIV treatment is ritonavir (Norvir, also in Kaletra).

A newer boosting agent is cobicistat. So far in North America cobicistat is found only inside a pill called Stribild. The purpose of cobicistat is to boost the concentration of elvitegravir so it can be taken just once daily. Stribild has to be taken with food, as this increases its absorption. Cobicistat is therefore very useful as a boosting agent, allowing for convenience and hopefully easier adherence. However, cobicistat interacts with many other medicines.
Enter dolutegravir

Dolutegravir is the third integrase inhibitor that’s been tested on a large scale for HIV treatment. There are several factors that make dolutegravir unique as an integrase inhibitor—it does not need a boosting agent and it can be safely taken once daily. Other factors concern its resistance profile, tolerability and anti-HIV activity, which we will explore in this issue of TreatmentUpdate.

Dolutegravir (sold under the brand name Tivicay) was approved in August in the U.S. and in October in Canada and is on track to be approved in the European Union and other countries.

B. Dolutegravir approved in Canada—what you need to know

The link below connects to a CATIE News story that has comprehensive information about dolutegravir in Canada. Also provided are details about drug interactions, side effects and other important information:


C. Dolutegravir vs. darunavir for the initial treatment of HIV

Darunavir (sold as Prezista) belongs to the class of HIV drugs called protease inhibitors. Darunavir is taken with a small dose of another protease inhibitor, ritonavir (Norvir), as ritonavir boosts darunavir levels in the blood so that once-daily dosing is possible. Taken this way, darunavir is a potent anti-HIV drug and an important part of treatment regimens for many HIV-positive people.

Researchers in the U.S and Europe conducted a study called Flamingo to assess the impact of dolutegravir-based combination therapy in the initial treatment of HIV infection. The comparison treatment in Flamingo was darunavir + ritonavir + two nukes (nucleoside analogues).

Results after one year suggest that both dolutegravir- and darunavir-based regimens are effective and generally safe. Dolutegravir-based regimens were found to be statistically superior to darunavir-based regimens. The implications of this and other findings are discussed later in this report.

Study details

Researchers analysed health-related data collected from HIV-positive participants who had never previously been treated and randomly assigned them to receive one of the following regimens once daily:

- dolutegravir 50 mg + two nukes
- darunavir + ritonavir + two nukes

The average profile of participants at the start of the study was as follows:

- gender – 85% men, 15% women
- age – 34 years
- CD4+ count – 400 cells
- HIV viral load – overall: 31,000 copies/ml; but 25% of participants had a viral load greater than 100,000 copies/ml
- hepatitis B virus co-infection – 3%
- hepatitis C virus co-infection – 7%

Distribution of nukes used:

- Truvada – a fixed-dose combination of tenofovir + FTC – 67%
- Kivexa – a fixed-dose combination of abacavir + 3TC – 33%

Flamingo is expected to continue for several years. We now report results from the first 48 weeks of the study.

Results

At week 48, the proportions of participants with a viral load less than 50 copies/ml were as follows:

- dolutegravir-based regimens – 90%
- darunavir-based regimens – 83%

As a greater proportion of dolutegravir users had a low viral load at week 48, researchers judged dolutegravir to be “statistically” superior to darunavir.

We will explore the implications of this finding of statistical superiority as well as side effects later in this report.
Results by initial viral load

Researchers analysed the data by the initial (baseline) viral load that participants had when they entered the study.

Among participants whose baseline viral load was high (more than 100,000 copies/ml), here are the proportions that had a viral load less than 50 copies/ml at week 48:

- dolutegravir-based regimens – 93% had a viral load less than 50 copies/ml
- darunavir-based regimens – 70% had a viral load less than 50 copies/ml

Among participants whose baseline viral load was less than 100,000 copies/ml, here are the proportions with less than 50 copies/ml at week 48:

- dolutegravir-containing regimens – 88%
- darunavir-containing regimens – 87%

Another way to examine the results is to look at the nukes used, as follows:

Kivexa
- Kivexa + dolutegravir – 90% of participants achieved a viral load less than 50 copies/ml
- Kivexa + darunavir – 85% of participants achieved a viral load less than 50 copies/ml

Truvada
- Truvada + dolutegravir – 90% of participants achieved a viral load less than 50 copies/ml
- Truvada + darunavir – 81% of participants achieved a viral load less than 50 copies/ml

Changes in CD4+ cell counts

Increases in CD4+ counts were similar between dolutegravir and darunavir users. On average, participants’ counts increased by 200 more cells at week 48.

Resistance and virological failure

Two participants in each treatment group initially suppressed their viral load below the 50 copy/ml mark, but then their viral load became greater than 200 copies/ml after week 24 of the study.

Side effects and complications

Here are some common side effects and their distribution:

Diarrhea
- dolutegravir-based regimens – 17%
- darunavir-based regimens – 29%

Nausea
- dolutegravir-based regimens – 16%
- darunavir-based regimens – 18%

Headache
- dolutegravir-based regimens – 15%
- darunavir-based regimens – 10%

The presence of any side effect of moderate-to-severe intensity was distributed as follows:

- dolutegravir-based regimens – 10%
- darunavir-based regimens – 12%

Here is the distribution of severely abnormal lab tests:

Cholesterol
- dolutegravir-based regimens – 0%
- darunavir-based regimens – 1%

LDL-C (so-called bad cholesterol)
- dolutegravir-based regimens – less than 1%
- darunavir-based regimens – 2%

ALT (alkaline aminotransferase; a liver enzyme)
- dolutegravir-based regimens – 1%
- darunavir-based regimens – 2%

Creatine kinase (an enzyme, elevated levels of which may be suggestive of muscle breakdown)
- dolutegravir-based regimens – 7%
- darunavir-based regimens – 4%

No deaths occurred because of the study drugs.

Why did statistical superiority occur?

Dolutegravir has powerful anti-HIV activity but so does darunavir when boosted with a small dose (100 mg) of ritonavir. Furthermore, the proportion of participants who did not respond virologically to therapy was similar and was distributed as follows:

- dolutegravir-based regimens – 6% did not achieve a viral load less than 50 copies/ml
- darunavir-based regimens – 7% did not achieve a viral load less than 50 copies/ml
In part, what appeared to drive the differing overall virological outcomes between the two regimens at week 48 was the number of participants who left the study prematurely. These participants were distributed as follows:

- dolutegravir-based regimens – 4% left the study prematurely
- darunavir-based regimens – 10% left the study prematurely

In clinical trials, participants leave a study prematurely for reasons such as adverse reactions (side effects, complications), death, because they moved and so on. Since the study drugs were not lethal and few patients changed residence, researchers were able to focus on adverse reactions as a reason for premature withdrawal from the study, distributed as follows:

- dolutegravir-based regimens – 1% left because of adverse reactions
- darunavir-based regimens – 4% left because of adverse reactions

These findings suggest that dolutegravir-based regimens were likely easier to tolerate.

One question that does not have a clear answer is this:

Does statistical superiority mean that dolutegravir is clinically superior to darunavir?

Boosted darunavir remains an important treatment option and may be a more forgiving regimen (requiring the development of multiple resistance mutations before treatment failure occurs), as is generally the case with other boosted protease inhibitor regimens. Yet, dolutegravir’s potency and relative simplicity (the lack of boosting) may make it an attractive option for some doctors and their patients.

In the future

A once-daily pill containing the following three medicines is under development: dolutegravir + abacavir + 3TC

REFERENCE:


D. Dolutegravir vs. raltegravir—results after two years

In a study called Spring-2, researchers in Canada, Australia, Europe and the U.S. recruited just over 800 HIV-positive volunteers to compare the effectiveness of a dolutegravir-based regimen to one based on the integrase inhibitor raltegravir (Isentress). Researchers found that after two years both integrase inhibitors were generally safe, well tolerated and effective. Side effects during the latter half of the study (weeks 48 to 96) were not common.

Study details

Research teams enrolled 822 volunteers who had never previously been exposed to anti-HIV drugs and randomly assigned them to receive one of the following regimens:

- dolutegravir 50 mg once daily + 2 nukes + placebo
- raltegravir 400 mg twice daily + 2 nukes + placebo

The nukes used in the study were as follows:

- Kivexa – a fixed dose combination of abacavir + 3TC
- Truvada – a fixed-dose combination of tenofovir + FTC

The average profile of participants at the start of the study was as follows:

- age – 36 years
- 86% men and 14% women
- CD4+ count – 360 cells
- HIV viral load – 35,000 copies/ml
- hepatitis B virus co-infection – 2%
- hepatitis C virus co-infection – 10%
- 60% of participants received Truvada
- 40% of participants received Kivexa

Results

As previously reported in TreatmentUpdate 194, (at the 48th week of the study researchers found that both regimens were roughly equal
in effectiveness (the technical term for this is statistically “non-inferior”) against HIV.

The proportions of participants at week 96 whose viral loads were less than 50 copies/ml were as follows:

- dolutegravir-based regimens – 81%
- raltegravir-based regimens – 76%

According to the researchers, the main reason for this difference was that more participants taking raltegravir left the study prematurely. Most of these participants left for reasons unrelated to adverse effects. One explanation for participants leaving the study prematurely was what the researchers called “virological failure.” They used this term to capture a number of situations, including the inability to suppress viral load below the 50-copies/ml mark and, in cases where it was suppressed, the inability to keep it below 50 copies/ml. The distribution of virological failure was as follows:

- dolutegravir-based regimens – 5%
- raltegravir-based regimens – 10%

**Resistance**

All participants who were taking dolutegravir-based regimens and who developed virological failure had viral loads less than 1,000 copies/ml. Indeed, most (77%) had a viral load more than 50 copies/ml but less than 200 copies/ml. None of these participants developed detectable resistance to any class of anti-HIV therapy.

Among participants taking raltegravir-based regimens who developed virological failure, while most (76%) had a viral load between 50 and 200 copies/ml, three had viral loads greater than 10,000 copies/ml. However, one participant had HIV that had mutated and developed resistance to integrase inhibitors and four other participants had HIV that had become resistant to nukes. This all occurred during the first year of the study.

In the second year of the study, development of detectable resistance mutations to any anti-HIV drug was comparatively uncommon.

The research team stated that “…the robustness of dolutegravir in the prevention of virological resistance is unique to the integrase inhibitor class and confers a specific advantage to this molecule.”

**Responses to therapy—initial CD4+ count**

Many factors could play a role in the response to HIV therapy and researchers involved with this study assessed the findings based on such factors as initial CD4+, initial viral load, and choice of nucleoside analogues (nukes) used.

The proportion of participants who responded well to dolutegravir-based regimens was generally good regardless of their initial (baseline) CD4+ cell count. However, participants with a low CD4+ cell count had poorer responses to both dolutegravir and raltegravir. This is likely because of their weaker overall health.

Here are the virological responses distributed by initial CD4+ count:

**Baseline CD4+ count less than 350 cells:**
- dolutegravir-based regimens – 78% subsequently achieved a viral load less than 50 copies/ml
- raltegravir-based regimens – 69% subsequently achieved a viral load less than 50 copies/ml

**Baseline CD4+ count less than 200 cells:**
- dolutegravir-based regimens – 71% subsequently achieved a viral load less than 50 copies/ml
- raltegravir-based regimens – 56% subsequently achieved a viral load less than 50 copies/ml

**Responses to therapy—initial viral load**

Among participants who had an initial viral load of 100,000 copies/ml or less, here are the proportions that subsequently achieved a viral load less than 50 copies/ml:

- dolutegravir-based regimens – 82% subsequently achieved a viral load less than 50 copies/ml
- raltegravir-based regimens – 82% subsequently achieved a viral load less than 50 copies/ml

Among participants whose initial viral load was greater than 100,000 copies/ml, here are the proportions that subsequently achieved a viral load less than 50 copies/ml:

- dolutegravir-based regimens – 78% subsequently achieved a viral load less than 50 copies/ml
- raltegravir-based regimens – 63% subsequently achieved a viral load less than 50 copies/ml
Responses to therapy—impact of nukes

Among participants who used Kivexa (abacavir + 3TC), here are the proportions that subsequently achieved a viral load less than 50 copies/ml:

- dolutegravir + Kivexa – 74% achieved a viral load less than 50 copies/ml
- raltegravir + Kivexa – 76% achieved a viral load less than 50 copies/ml

Among participants who used Truvada (tenofovir + FTC) here are the proportions that subsequently achieved a viral load less than 50 copies/ml:

- dolutegravir + Truvada – 86% achieved a viral load less than 50 copies/ml
- raltegravir + Truvada – 76% achieved a viral load less than 50 copies/ml

Tolerability

The safety of both dolutegravir- and raltegravir-containing regimens was good, with generally similar rates of reported adverse events (side effects and complications). Most side effects occurred during the first year of the study.

No participant taking dolutegravir in the second year of the study left prematurely because of side effects. However, three participants who were taking raltegravir had to stop due to side effects.

Side effects reported in the second year of the study were usually of mild or moderate intensity. Adverse events reported at week 96 were distributed as follows:

Nausea
- dolutegravir-containing regimens – 15%
- raltegravir-containing regimens – 14%

Headache
- dolutegravir-containing regimens – 14%
- raltegravir-containing regimens – 13%

Stuffy nose and/or sore throat
- dolutegravir-containing regimens – 13%
- raltegravir-containing regimens – 14%

Diarrhea
- dolutegravir-containing regimens – 14%
- raltegravir-containing regimens – 13%

No deaths related to the study medicines occurred.

Changes in lab test results

Researchers did not find any clinically meaningful changes in levels of cholesterol in the blood of participants during the study.

Focus on the kidneys

Dolutegravir users had small increases in their level of creatinine (a waste product formed from the breakdown of muscle) in their blood as follows:

- week 48 – an average increase of 12 micromol/Litre
- week 96 – an average increase of 15 micromol/Litre

These small but sustained changes in creatinine occurred because dolutegravir interferes with the kidneys’ ability to remove creatinine from the blood. The change appears to be harmless. For instance, researchers conducted additional and more direct tests of kidney health—focusing on the ratio of the protein albumin to creatinine in the blood—and did not find any significant differences in this ratio between dolutegravir and raltegravir users.

The small interference with creatinine release into the urine is also seen with other drugs, such as in these cases:

- the anti-ulcer agent cimetidine (Tagamet; available over the counter)
- the antibiotic trimethoprim (in Bactrim/Septra)
- the anti-HIV drug rilpivirine (Edurant and in Complera)
- the boosting agent cobicistat (in Stribild)

In such cases, the small increase in creatinine that occurs when these drugs are used does not appear to cause harm.

Heart health

Overall, the researchers did not find any differences in changes in heart beat or abnormal heart rhythms in participants. However, one participant taking dolutegravir had a slightly abnormal heart rhythm.

As with all the clinical trials of dolutegravir, there have not been any reports of increased risk of heart attacks in participants in general and in users of abacavir in particular. This latter finding is consistent with an analysis of abacavir done by
the U.S. Food and Drug Administration (FDA), which reviewed many randomized clinical trials and found no increased risk of cardiovascular complications in people who had used the drug.

Summary

In analysing the two-year data on dolutegravir-based regimens, researchers have found that this drug, when taken in a dose of 50 mg once daily, was as effective and safe as twice-daily raltegravir-based regimens. Results with dolutegravir were similar regardless of initial viral load or the additional nukes used in regimens—abacavir + 3TC or tenofovir + FTC.

Dolutegravir and raltegravir caused a relatively low rate of side effects; when they did occur, such side effects were generally of mild-to-moderate intensity. This is similar to what has been seen in other trials of dolutegravir.

Other trials with dolutegravir are ongoing, including a clinical trial in women called Aria.

REFERENCES:


E. Resistance to integrase inhibitors

HIV has the ability to mutate (or change) and develop the capacity to resist the effects of treatment. The chance of such changes greatly increases when doses of treatment are missed or skipped.

Researchers in North Carolina have been studying HIV’s ability to resist treatment, particularly the class of medicines called integrase inhibitors. Members of this class are as follows:

- raltegravir
- elvitegravir
- dolutegravir

In this recent study, U.S. researchers analysed HIV in blood samples from 3,022 participants that had been collected to assess HIV’s ability to resist drugs. The type of resistance testing done was genotypic testing. This type of testing can identify known mutations in genes that allow HIV to resist the effect of therapy.

Resistance to integrase inhibitors

Researchers found that about 16% of participants had HIV with at least one major mutation in the integrase gene. Common mutations were as follows:

- N155H
- Q148H/K/R

These mutations were equally common.

Based upon these and other findings, the researchers predicted that high-level resistance (this would very likely lead to treatment failure) to the following drugs was present in the following proportion of participants in their study:

- raltegravir – 15% of participants had high-level resistance to this drug
- elvitegravir – 13% of participants had high-level resistance to this drug
- dolutegravir – 2% of participants had high-level resistance to this drug

The 2% figure above was derived from all 3,022 participants. However, among participants who had at least one major mutation to integrase inhibitors, 12% had high-level resistance to dolutegravir. In other words, it is very likely that dolutegravir would not have been an effective treatment option for these people because of the development of cross-resistance.

About cross-resistance

Bear in mind that exposure to a failing regimen containing an integrase inhibitor can, in some cases, lead to the development of mutations in HIV that can cause not only resistance to the integrase inhibitor being used but also cross-resistance to other integrase inhibitors that have not yet been used. In the present study, some people using raltegravir not only developed resistance to this drug but also cross-resistance to other integrase inhibitors—even though they had never used these other drugs (elvitegravir and, to a lesser extent, dolutegravir). Cross-resistance is also an issue with other classes of HIV drugs.
The study took place over four years between January 2009 and December 2012. During this time, raltegravir is likely the integrase inhibitor that patients would have used. Elvitegravir was only approved four months prior to the study, so it is unlikely that elvitegravir users would have been part of it. Also, because anyone who participated in a clinical trial of integrase inhibitors was excluded, it is extremely unlikely that anyone in the study was exposed to dolutegravir, which was only approved in the U.S. in August 2013.

Additional findings

Researchers found that there were 239 participants with a high degree of resistance to integrase inhibitors. These participants were very treatment experienced, and HIV resistance testing revealed that they appeared to have limited treatment options. Among these 239 participants, here are some additional results of resistance testing:

- nukes – 14% did not have a nuke that was fully active against HIV
- non-nukes – 27% did not have a non-nuke that was fully active against HIV
- protease inhibitors – 5% did not have a protease inhibitor that was fully active against HIV

Overall, the study’s findings underscore the need to screen patients for resistance testing, particularly those whose integrase-based regimens may be failing.

CATIE’s *Positive Side* magazine has a very useful resource to help people understand HIV and its ability to resist therapy:


REFERENCE:

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