Dolutegravir approved in Canada—what you need to know

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On October 31, 2013, Health Canada licensed the sale and use of a new anti-HIV drug called dolutegravir. This drug will be sold under the brand name Tivicay and is made by the pharmaceutical company ViiV Healthcare. Dolutegravir is already licensed in the U.S. and approval is pending in the European Union and Australia.

Dolutegravir belongs to the class of drugs called integrase inhibitors and is meant to be used as part of combination therapy for the treatment of HIV; such therapy is commonly called ART or HAART.

For most patients, dolutegravir can be taken at a dose of 50 mg once daily. This drug does not have any food or water restrictions and it can be taken day or night. Dolutegravir was relatively well tolerated in clinical trials. When side effects occurred, they were generally mild. Further details on side effects appear later in this CATIE News bulletin.

Studies

In clinical trials where dolutegravir was used as part of initial therapy for HIV, dolutegravir-based combinations have been very effective in reducing the amount of HIV in the blood (viral load) and improving the health of the immune system by increasing the number of CD4+ T-cells.

In HIV-positive people who are treatment experienced but who were not previously exposed to integrase inhibitors, clinical trials have found that dolutegravir can be very effective and in some cases better than existing regimens.

In HIV-positive people who are treatment experienced and who have HIV that is somewhat resistant to integrase inhibitors, dolutegravir-based regimens have, in most cases, been able to greatly reduce the amount of HIV in the blood.

In a study called Viking, researchers enrolled 51 HIV-positive people who were highly treatment experienced and who were using, or who had previously used, the integrase inhibitor raltegravir (Isentress). All participants were either experiencing treatment failure with raltegravir-based regimens or had HIV that was resistant to raltegravir when they enrolled in the study. Furthermore, the majority of participants had HIV that was resistant to many other anti-HIV drugs. Researchers used resistance testing to find the best possible background therapy for participants and then added dolutegravir (50 mg once or twice daily) to their regimens. Overall results six months later showed that participants who took dolutegravir 50 mg twice daily had the best response, with 75% having a viral load of less than 50 copies/ml (compared to 41% taking dolutegravir once daily). In general, dolutegravir was well tolerated.

Looking more closely at the data, the virologic response was better in participants who had a greater number of active anti-HIV drugs in their regimen. In other words, participants who had HIV that was susceptible to more drugs did better than participants who had HIV that was susceptible to fewer drugs.

Common side effects

In clinical trials, dolutegravir, like all integrase inhibitors, was well tolerated, generally safe and effective. However, as with any treatment, there were side effects that users should be aware of. The most common side effects were as follows:

- headache
• difficulty falling asleep
• nausea
• diarrhea

Bear in mind that, like all new drugs, as dolutegravir becomes more widely used in the community, there may be reports of other side effects.

The kidneys

The kidneys filter the blood and then put waste materials into urine and reabsorb nutrients and other useful materials back into the blood.

Dolutegravir can interfere with the ability of the kidneys to release the waste product creatinine into urine. Therefore, a small but persistent increase of creatinine levels in the blood is generally seen in dolutegravir users. This small increase is not considered harmful. Furthermore, this effect on creatinine does not appear to affect the ability of the kidneys to filter other substances. Such an effect on creatinine is also seen with the anti-ulcer drug cimetidine (Tagamet) and with the boosting agent cobicistat, found in Stribild.

Uncommon side effects

Hypersensitivity reactions occurred in less than 1% of participants in phase III clinical trials. Symptoms included severe rash or rash with a fever, together with lack of energy and painful muscles or joints. In severe cases additional symptoms occurred, such as peeling of the skin, blisters on the lips, swollen eyes and face, stomach cramps and difficulty breathing. ViiV Healthcare advises that dolutegravir (or any other drugs suspected of causing this reaction) should be discontinued immediately if these symptoms occur, otherwise the hypersensitivity reaction can become life threatening. In the rare cases of a hypersensitivity reaction to dolutegravir, ViiV advises that this drug should not be restarted.

Women

In clinical trials with dolutegravir, about 15% of participants were women. ViiV is enrolling women for a clinical trial designed to specifically study the effect of dolutegravir in this population.

Dolutegravir’s safety in pregnant women is not known. Therefore, ViiV recommends that dolutegravir should only be used in pregnancy if “the potential benefit justifies the potential risk.”

Hepatitis B or C viruses

People who are co-infected with hepatitis B or C viruses may develop increased levels of liver enzymes in the blood or intensified symptoms of infection with these viruses. Therefore, ViiV advises doctors to conduct “appropriate” laboratory testing before and during therapy with dolutegravir and to monitor patients for liver injury.

Understanding drug interactions

Sometimes one drug can interfere with the body’s processing of another drug. Such an effect is called a drug–drug interaction or, more simply, a drug interaction. This can result in higher-than-normal levels of one or both drugs in the blood, resulting in side effects or worsening of pre-existing side effects. Alternatively, the interference of one drug on another can cause the levels of one or both drugs to fall below normal levels. This can result in the drug(s) losing effectiveness. In the case of HIV meds, this fall in drug level(s) can help HIV develop the ability to resist one drug and, likely, other related drugs. This resistance limits future treatment options.

To minimize the development of resistance, all prescribed medicines should be taken every day, exactly as directed.

Always tell your doctor and nurse about all the drugs you are taking, both prescription and over the counter as well as any supplements or herbs. Pharmacists can be very helpful in checking for the possibility of drug interactions.

Dolutegravir and drug interactions

In general, integrase inhibitors tend not to interfere with many other drugs (raising or lowering their levels in the
Dolutegravir causes few interactions with other drugs. However, there are other medicines that interfere with dolutegravir levels in the blood, usually decreasing them. Bear in mind that as dolutegravir becomes more widely used in the community, there may be reports of new drug interactions.

Here are recommendations from Viiv about potentially significant drug interactions with dolutegravir:

**Other HIV drugs**

Etravirine (Intelence) – this drug can reduce the concentration of dolutegravir in the blood. Therefore, Viiv recommends that dolutegravir should not be used with etravirine unless it is also taken with one of the following combinations of drugs:

- atazanavir (Reyataz) + ritonavir (Norvir)
- darunavir (Prezista) + ritonavir
- lopinavir + ritonavir (in Kaletra)

Nevirapine (Viramune) – dolutegravir should not be used with nevirapine, as there is not enough information to make dosing recommendations.

**Acid-reducing agents, laxatives and buffered medicines**

Dolutegravir should be taken 2 hours before or 6 hours after taking these medicines.

**Abnormal heart rhythm drugs**

The drug dofetilide (Tikosyn) is prescribed to treat abnormal heart rhythms. Dolutegravir can raise levels of dofetilide. Although dofetilide is not approved in Canada, many Canadians travel to the U.S. where it is approved and may be prescribed this medicine. Viiv warns that dofetilide should never be used by patients who are taking dolutegravir, as high concentrations of dofetilide can occur causing serious injury.

**Anti-seizure drugs**

Oxcarbazepine, carbamazepine (Tegretol), phenobarbital, phenytoin (Dilantin) – dolutegravir should not be used with these drugs as there is not enough information to make dosing recommendations.

**Antibiotics**

Rifampin – this drug reduces the concentration of dolutegravir in the blood. Viiv recommends that dolutegravir at a dose of 50 mg twice daily should be used if rifampin must also be taken. However, Viiv also notes that in the case of patients who have used integrase inhibitors in the past and who have HIV that may be or is suspected to be resistant to integrase inhibitors, doctors and nurses should seek alternative antibiotics to rifampin where possible.

**Diabetes drugs**

Metformin – as dolutegravir can raise levels of metformin in the blood, Viiv recommends close monitoring of patients when they are starting or stopping therapy with dolutegravir. Viiv also suggests that it may be necessary to reduce the dose of metformin in some dolutegravir users.

**Herbs**

St. John’s wort (or compounds found in St. John’s wort such as hypericin, hyperforin) can significantly reduce dolutegravir levels and this herb should not be used. Although St. John’s wort is the only herb listed here, note that other herbs are likely to interact with dolutegravir.

**No interactions expected**

In clinical trials, dolutegravir did not have a clinically significant effect on the following drugs:

- tenofovir (Viread and in Truvada, Atripla, Complera and Stribild)
A note on resistance testing

The United States Department of Health and Human Services (DHHS) has been producing guidelines that have been at the forefront of helping to improve the care and treatment of HIV-positive people for many years. In November 2013, the DHHS revised its guidelines.

One of those revisions notes that for patients whose integrase inhibitor regimens are failing, doctors should request laboratory testing of their blood to assess the degree of resistance to integrase inhibitors. This will help doctors determine whether or not an integrase inhibitor can be used in future regimens.

A study in the U.S. with about 3,000 HIV-positive participants who were undergoing testing of their blood for the presence of HIV resistance has recently been completed. Researchers found that resistance to integrase inhibitors was present in 16% of participants. Their results suggested that, in most cases, dolutegravir would have “full or partial activity” against most strains of HIV with integrase resistance. However, 2% of all participants (or 12% of participants with HIV resistant to the integrase inhibitors raltegravir or elvitegravir) had “high-level resistance to dolutegravir.”

The role of dolutegravir and other integrase inhibitors

The DHHS has also recommended that all of the licensed integrase inhibitors can now be listed as a preferred drug (each integrase inhibitor has equal status and is listed in order of their regulatory approval) when used in the following regimens:

- raltegravir 400 mg twice daily + Truvada (tenofovir + FTC) once daily
- Strivid (containing the integrase inhibitor elvitegravir, Truvada and the boosting agent cobicistat) once daily in patients who have good kidney function
- dolutegravir 50 mg once daily + Kivexa (abacavir + 3TC) once daily in patients who are HLA B*5701 negative
- dolutegravir 50 mg once daily + Truvada once daily

Notes:

1. The DHHS recommends that Strivid only be used in patients whose kidneys are in relatively good health; that is, those who have an eGFR (estimated glomerular filtration rate) of 70 mL/min or higher.
2. HLA B*5701 testing refers to a simple blood test to assess whether patients are likely to develop a hypersensitivity reaction to abacavir, a medicine contained in Kivexa.

Dosing

Dolutegravir has been approved for use in people aged 12 years and older and who weigh at least 40 kg (88 pounds). It can be taken with or without food. There are two general dosing regimens for dolutegravir recommended by ViIV, as follows:

- People who have never previously used ART – 50 mg once daily
- People who have used ART but have never used an integrase inhibitor – 50 mg once daily
- People who have used integrase inhibitors and who have or are suspected to have resistance to other integrase inhibitors – 50 mg twice daily
- People who are taking any of these drugs (regardless of previous exposure to integrase inhibitors): efavirenz, fosamprevir + ritonavir, tipranavir (Aptivus) + ritonavir, and rifampin – 50 mg twice daily

The long and winding road

Once Health Canada approves a drug, physicians can prescribe it but patients must pay for it unless their private
insurance plan provides coverage. If left untreated, HIV infection leads to catastrophic disease that can affect people's ability to work and requires expensive care. In Canada, provincial and territorial ministries of health heavily subsidize the cost of anti-HIV medications. Each ministry has a listing of drugs for which it is prepared to pay. These listings are called formularies.

After federal approval, each HIV medicine must undergo another review process called Common Drug Review (CDR). As part of this review, recommendations are made as to whether the drug in question should be:

- listed on formularies
- listed on formularies with conditions, which means its use is restricted
- not listed at all

The CDR may also result in no decision being made as additional information is gathered. With the exception of Quebec, all provinces and territories, the Departments of National Defence and Veterans Affairs, and the Non-Insured Health Benefits plan participate in the CDR.

Dolutegravir will undergo the CDR process in 2014 with the results available later that year.

**In Quebec**

ViiV plans to submit a dossier on dolutegravir to L’Institut national d’excellence en santé et en services sociaux (INESSS) shortly. Dolutegravir will hopefully be listed on the Quebec formulary—Liste des médicaments assurés du Québec—in 2014.

**Patients on the dolutegravir expanded access program**

ViiV has a small number of patients in Canada with multidrug-resistant HIV whose doctors have been able to secure dolutegravir for them. ViiV will continue to supply dolutegravir to these patients until provincial formularies agree to pay for the drug.

**Cost**

At press time we do not have information on the cost of dolutegravir in Canada. However, as Ministries of Health tend to negotiate a reduced price in exchange for listing a drug on their formularies, we expect that dolutegravir-containing regimens are likely to have similar prices to other commonly used regimens already on provincial and territorial formularies.

**Availability**

Dolutegravir will be available as a small 50-mg yellow tablet. Pharmacies will be able to place orders for dolutegravir in a few weeks and the company will ship them the drug shortly thereafter.

**For the future**

ViiV Healthcare is also developing a pill containing the following three anti-HIV medicines:

- dolutegravir
- abacavir (Ziagen, and in Kiveza and Trizivir)
- 3TC (lamivudine, and in Kivexa and Trizivir)

The all-in-one pill containing dolutegravir will likely take another year before it is approved in the U.S., Canada and elsewhere.

---Sean R. Hosein

**REFERENCES:**


Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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