A. Genvoya approved—What you need to know

On November 27, 2015, Health Canada licensed the sale and use of a new anti-HIV treatment sold under the brand name Genvoya and made by the pharmaceutical company Gilead Sciences. Genvoya is a complete treatment in one pill that comes in the form of green capsule-shaped tablets. The dose of Genvoya used by adults with HIV is one tablet once daily with food. Genvoya was generally well tolerated in clinical trials; general and usually temporary side effects included headache, tiredness or lack of energy, nausea and diarrhea. Genvoya should be available for ordering by pharmacies late in January 2016.

Inside Genvoya

Each tablet of Genvoya contains the following medicines:

- elvitegravir 150 mg – an integrase inhibitor
- cobicistat 150 mg – a boosting agent; cobicistat raises and maintains the level of elvitegravir in the blood so that it can be taken only once a day
- FTC (emtricitabine) 200 mg – a nucleoside analogue (nuke) that works against HIV
- TAF (tenofovir alafenamide) 10 mg – another nuke that works against HIV

The only new drug listed above is TAF. This is a new formulation of an older drug called tenofovir DF (tenofovir disoproxil fumarate). TAF is meant
to eventually replace tenofovir DF. In clinical trials, TAF was found to be safe and generally well tolerated with fewer side effects than tenofovir DF. Further details on side effects appear later in this issue of *TreatmentUpdate*.

Genvoya is the first pill to be licensed in Canada that contains TAF.

**Studies**

In clinical trials (for details, see *TreatmentUpdate* 211) Genvoya has been tested in more than 3,000 HIV-positive people. Researchers found that Genvoya was an effective regimen against HIV. Genvoya, which contains TAF, was found to be as good as other regimens that contained the older formulation, tenofovir DF. Genvoya was generally well tolerated and safe; because it contains TAF, it has a reduced potential for causing side effects affecting the kidney and bones compared to regimens that include tenofovir DF. Genvoya was effective both in people new to anti-HIV therapy and in those who are treatment-experienced.

**Common side effects**

In clinical trials Genvoya was generally well tolerated. General side effects included the following:

- headache
- tiredness or lack of energy
- nausea
- diarrhea

These side effects are usually temporary.

**Uncommon side effects**

Fewer than 1% of participants in clinical trials experienced the following side effects:

- abdominal pain
- indigestion
- flatulence
- rash
- vomiting

**The kidneys**

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

Genvoya, because it contains cobicistat, 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 people who use Genvoya. This small increase is not considered harmful and is usually reversible once a person stops taking Genvoya. Furthermore, this particular effect on the kidneys does not appear to affect the ability of these organs to filter other substances. This effect on the kidneys by cobicistat is also seen with the anti-ulcer drug cimetidine (Tagamet) and the anti-HIV drug dolutegravir (Tivicay and in Triumeq).

**Lipid levels**

In clinical trials Genvoya users developed small increases in the levels of cholesterol and triglycerides in their blood.

**Warnings**

1. **Lactic acidosis**

Genvoya contains TAF and FTC. Both of these medicines may be associated with a build-up of the waste product lactic acid in the blood. People who are obese or who have used nukes for many years may be at increased risk of developing lactic acidosis. Symptoms of excess amounts of lactic acid in the blood can include the following:

- nausea
- vomiting
- abdominal pain
- diarrhea
- unexpected tiredness
- unexpected muscle pain
- feeling cold, especially in the arms and legs
- feeling dizzy or light-headed

If these symptoms occur while you are taking Genvoya, call your doctor right away.

2. **Liver problems—enlarged liver and fatty liver**

In rare cases, people who take Genvoya may develop swollen liver (hepatomegaly) or fatty
liver (steatosis). Obesity and the use of nukes over many years may be risk factors for enlarged and fatty liver in people with HIV. People who develop these specific liver problems may also develop the following symptoms:

- yellowing of the skin and whites of the eyes (jaundice)
- nausea
- vomiting
- abdominal pain

If any of these symptoms develop, contact your doctor right away.

### 3. Other liver problems—hepatitis viruses

The safety of Genvoya in people co-infected with HIV and hepatitis B virus (HBV) is not known. Genvoya contains tenofovir (in the form of TAF), which has anti-HBV activity. Co-infected people who take Genvoya and then stop it may notice symptoms of their hepatitis B infection worsen. If you have this co-infection, talk to your doctor before you start Genvoya. If you later need to change your therapy, remind your doctor that you have hepatitis B.

People who are co-infected with HIV and hepatitis-causing viruses (including hepatitis C virus) and who take potent combination anti-HIV therapy (ART) can be at increased risk for liver injury. It is important to have regular blood tests so that your doctor can assess the health of your liver. If lab tests reveal that you do not have hepatitis B, speak to your doctor about getting a vaccine to protect you from it. There is no vaccine for preventing hepatitis C virus infection.

### 4. Women

In clinical trials with Genvoya, the proportion of women enrolled was relatively small. However, no side effects were more common in women than in men.

Genvoya’s safety has not been studied in pregnant women. Gilead Sciences recommends: “Genvoya should not be used in pregnant women unless the potential benefits outweigh the potential risks to the fetus.”

### 5. Emotional issues—anxiety and depression

Genvoya is similar to another fixed-dose combination treatment called Stribild (the only difference between these pills is that Genvoya contains TAF, and Stribild contains tenofovir DF instead of TAF). After the licensure of Stribild, reports emerged of very rare cases of depression associated with the use of Stribild. Stribild and Genvoya both contain the integrase inhibitor elvitegravir. Note that all integrase inhibitors have been associated with rare cases of anxiety and depression. Whether these drugs caused anxiety or depression is not clear. In some reports, the rare cases of anxiety and/or depression associated with the use of integrase inhibitors occurred mainly in people who had a history of these issues.

Anxiety and depression are relatively common in HIV-positive people (regardless of whether they are on treatment or the type of treatment that they take). If you are taking Genvoya and think that you may have developed anxiety or depression, speak to your doctor right away. Your doctor can help determine if you have anxiety or depression and if there is any relationship between them and the medicines that you are taking.

If you have thoughts of harming yourself or others, dial 911 right away.

### 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 cause 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 anti-HIV meds, this fall in drug levels can cause HIV to develop the ability to resist one drug and, likely, other related drugs. This drug resistance limits future treatment options.

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

Always tell your doctor, nurse and pharmacist about all the drugs you are taking—prescription and over the counter, supplements or herbs, and street drugs. Pharmacists in particular can be very helpful in checking for the possibility of drug interactions.
Genvoya and drug interactions

Gilead Sciences recommends that the following medicines NEVER be used by someone who is taking Genvoya because they could lead to serious or life-threatening effects or they can weaken the anti-HIV activity of Genvoya:

- anti-asthma drugs – salmeterol (Advair, Serevent)
- antihistamines – astemizole, terfenadine
- anti-tuberculosis (TB) drugs – rifampin
- anti-migraine drugs (ergot derivatives) – dihydroergotamine (Migranal), ergotamine (Ergomar), ergonovine, methylergonovine
- anti-anxiety drugs – midazolam (Versed), triazolam (Halcion)
- anti-seizure drugs – carbamazepine, phenobarbital, phenytoin
- gastrointestinal motility drugs – cisapride (Prepulsid)
- antifungal drugs – voriconazole (Vfend), posaconazole (Posanol)
- antipsychotic drugs – pimozide (Orap)
- herbs – St. John’s wort and its extracts (such as hypericin and hyperforin)
- cholesterol-lowering medicines (statins) – lovastatin and simvastatin
- drugs for prostate problems – alfuzosin
- drugs for pulmonary hypertension – Revatio (sildenafil)

Commonly used drugs and their interactions

Acid-reducing agents can lower levels of elvitegravir (in Genvoya) if taken at the same time as Genvoya. Therefore, Gilead Sciences recommends that you take Genvoya and antacid “at least two hours” apart from each other.

Genvoya can raise the level of erectile dysfunction drugs—such as sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra)—in the blood, leading to side effects. Gilead provides the following advice for dosing these drugs in Genvoya users:

- sildenafil – no more than 25 mg in a 48-hour period should be used
- tadalafil – no more than 10 mg in a 72-hour period should be used
- vardenafil – no more than 2.5 mg in a 72-hour period should be used

Other drug interactions

In some cases, with advice and monitoring by your doctor and the use of lab and other tests, it can be possible for you to use some of the drugs listed below. Your doctors, including in some cases your specialist and pharmacist, can advise you how to take Genvoya safely with these drugs. The following drugs can interact with Genvoya and/or vice versa:

- abnormal heart rhythm drugs – amiodarone, bepridil, digoxin, disopyramide, flecainide, systemic lidocaine, mexiletine, propafenone, quinidine
- antibiotics – clarithromycin (Biaxin) and telithromycin
- some antidepressants
- antifungal agents – itraconazole, ketoconazole, voriconazole
- cholesterol drugs – atorvastatin, lovastatin, voriconazole
- corticosteroids (inhaled) – fluticasone
- corticosteroids (systemic) – dexamethasone
- hormonal contraceptives (the Pill) – norgestimate + ethinyl estradiol
- drugs to prevent blood clots – warfarin
- drugs to treat higher-than-normal blood pressure – amlodipine (Norvasc), diltiazem (Cardizem, Tiazac), felodipine, isradipine, nicardipine (Cardene SR), nifedipine (Procardia), nisoldipine (Sular), verapamil (Calan, Verelan, Covera-HS)
- drugs to treat pulmonary arterial hypertension (PAH) – bosentan
- hepatitis C treatments – Harvoni (sofosbuvir + ledipasvir), boceprevir
- sedatives – buspirone, zolpidem (Ambien)
- anti-TB drugs – rifabutin or rifapentine

Gilead notes that the following drugs do not have any “clinically significant interactions” with Genvoya:

- entecavir
- famciclovir
- methadone
- ribavirin
- sertraline

Resistance and other integrase inhibitors

Genvoya is meant to be taken once daily every day with food. If you have problems taking Genvoya exactly as directed, speak to your doctor and
pharmacist. They can help you find ways to stick to your drug regimen. If you do not take Genvoya once every day, the level of anti-HIV drugs in your body will be reduced. When this happens, HIV can develop the ability to resist the medicines that make up Genvoya, which means that the medicines will no longer work. This could weaken your immune system and affect your body’s ability to fight infections. Also, the development of HIV that is resistant to one or more of the medicines inside Genvoya can reduce your future treatment options.

The U.S. Department of Health and Human Services (DHHS) has been producing comprehensive HIV treatment guidelines for many years. These guidelines recommend that patients have resistance testing done prior to starting ART. Such testing can help reveal if HIV in your body has any resistance to the drugs in Genvoya.

Genvoya contains the integrase inhibitor elvitegravir. HIV that is resistant to elvitegravir is also usually resistant to another integrase inhibitor called raltegravir (Isentress). HIV that is resistant to elvitegravir or raltegravir is usually sensitive to another integrase inhibitor, dolutegravir (Tivicay and in Triumeq). Only a combination of resistance testing of a sample of your blood and a review of your treatment history can help your doctor determine which treatments are best for you.

Dosing

Gilead Sciences recommends that adults and adolescents who are at least 12 years and who weigh at least 35 kg can use Genvoya.

The recommended dose is one tablet once daily with food. The type of food does not matter.

Gilead Sciences advises the following when it comes to missed doses: If you miss “a dose of Genvoya within 18 hours of the time it is usually taken, [you] should take Genvoya with food as soon as possible, and then take the next dose of Genvoya at the regularly scheduled time.” But, if you miss a dose of Genvoya “by more than 18 hours, [you] should not take the missed dose but resume the usual dosing schedule.”

Access

Once Health Canada licenses a drug, physicians can prescribe it but patients must pay for it unless they have a private insurance plan that provides coverage. If left untreated, HIV infection leads to catastrophic disease that can affect one’s ability to work and requires expensive care. Therefore, 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.

In the months ahead, Gilead Sciences and provincial and territorial formularies will be negotiating the price of Genvoya. Your pharmacist or doctor can tell you when Genvoya is listed on your region’s formulary.

REFERENCES:
B. Dolutegravir—A powerful drug entering different research paths

Dolutegravir, sold as Tivicay and in a pill called Triumeq (containing dolutegravir + abacavir + 3TC), belongs to a class of anti-HIV drugs called integrase inhibitors. These drugs, when used as part of potent combination anti-HIV therapy (commonly called ART), can quickly reduce the amount of HIV in the blood. Other licensed integrase inhibitors are elvitegravir (found in Genvoya and Stribild) and raltegravir (Isentress).

Dolutegravir-based regimens have performed very well in clinical trials, showing good general safety and either rough equivalence or statistical superiority to other leading regimens. Dolutegravir derives its potency, in part, because it binds very tightly to a viral enzyme called integrase. This enzyme is needed by HIV to help the virus insert its genetic material into a cell’s DNA. Minor changes, or mutations, in integrase generally do not stop dolutegravir from binding to HIV. Furthermore, dolutegravir seems to bind to integrase for a relatively long period of time (hours). The relatively long time that dolutegravir binds to integrase may make it difficult for HIV to develop high-level resistance, particularly in people who are using dolutegravir-based ART for the first time, provided they take ART every day, exactly as directed.

Clinical trials ahead

Dolutegravir’s advantages in clinical trials—its relative potency, safety, once-daily dosing (in people who have not taken ART before), lack of food restrictions and limited drug interactions—have caused researchers to theorize about different ways of using the drug. For instance, because dolutegravir is so powerful, some researchers are seeking to test this drug in simplification studies. In such studies, regimens are simplified from the usual four or three drugs to two or even one drug alone.

Caution needed

While dolutegravir is indeed powerful, it is not invincible. If used improperly, treatment failure can occur, particularly in people who have previously used integrase inhibitors. Therefore, simplification regimens are best pursued by entering clinical trials. We will have details from some simplification studies later in this issue of TreatmentUpdate. These trials should be viewed as pilot studies or providing preliminary results because they are generally small and of short duration (six to 12 months). They may provide interesting results, but such results require confirmation in a larger trial of more robust statistical design.

Dolutegravir’s power has also intrigued some researchers to move in the opposite direction of simplification—intensification. In such studies, standard ART regimens are intensified by adding dolutegravir. Researchers at the Alfred Hospital in Melbourne, Australia, and elsewhere are planning such intensification studies.

REFERENCES:


C. Caution needed when interpreting the results of simplification studies

There is much excitement from researchers about finding new ways to use dolutegravir (Tivicay and in Triumeq). In this issue of TreatmentUpdate we present some results from small and generally short simplification trials with dolutegravir (and other drugs). However, because of their design, these studies raise many issues, which have yet to be addressed. Here are some examples:

• What is the long-term effectiveness of dolutegravir monotherapy?
• In people who use potent combination anti-HIV therapy (ART), HIV continues to infect cells and replicate at low levels in lymph nodes and lymphatic tissue. Some researchers think that this continued replication in lymphatic tissues is one of the reasons ART is unable to cure HIV. What happens in these locations with simplified therapy?
• HIV affects the brain. Is simplified therapy with dolutegravir sufficient to maintain a person’s neurocognitive abilities?
• HIV-positive people who use ART and maintain an undetectable viral load in the blood and who do not have sexually transmitted infections are highly unlikely to sexually spread HIV. Is simplified therapy with dolutegravir able to suppress levels of HIV in the genital tract?
• Is simplified therapy with two drugs, such as dolutegravir + 3TC, equivalent in potency to therapy with dolutegravir + two other drugs?
• Does the reservoir, or burden, of HIV-infected cells increase, decrease or stay the same with simplification therapy?
• HIV is associated with inflammation and activation of the immune system, even in people who take ART. This inflammation/activation may increase the risk for complications over the long term. What effect does simplification therapy have on inflammation/activation of the immune system?

Until robustly designed clinical trials can provide clear answers to these and other related questions, we urge our readers to be cautious about interpreting the preliminary results from simplification therapy that they may hear or read about. Furthermore, treatment guidelines in Canada and the U.S. do not recommend the use of such simplified therapy with dolutegravir.

REFERENCES:

D. Montreal researchers plan to explore dolutegravir’s effect on the HIV reservoir

For the past several decades, the laboratory of McGill University professor Mark Wainberg, PhD, has been studying HIV and how this virus changes (or mutates) so that it can resist the effect of different anti-HIV drugs.

A research associate at the Wainberg lab, Thibault Mesplède, PhD, has become interested in how HIV-infected cells are affected by one particular drug—dolutegravir (Tivicay and in Triumeq). Wainberg, Mesplède and their associates are conducting experiments in the lab to better understand the interaction between HIV-infected cells and dolutegravir. To do this, they keep cells of the immune system alive and proliferating (making new cells) and add a mix of nutrients, liquids, HIV and dolutegravir. They observe and detect changes in HIV’s genetic material over time.

In analysing their experiments, they have found that it is extremely difficult to find HIV that has
developed high-level resistance to dolutegravir. Bear in mind that these are the results of carefully controlled lab experiments and not work from studies in HIV-positive people. (Later in this issue of Treatment Update we report on cases of treatment failure with dolutegravir in people.) The findings from laboratory research have spurred Mesplède to design experiments that will use dolutegravir as a probe in order to try to better understand if this drug might have an effect on the body’s pool of HIV infected cells. This pool is also called the reservoir. Researchers in Canada and at leading scientific institutes in other countries are designing experiments that aim to measure the size of the reservoir and uncover ways to shrink the reservoir. It is possible that if Mesplède’s initial work is successful dolutegravir could play a role in some of these experiments.

Resistance and the reservoir

In some people, HIV has developed the ability to partially or wholly resist the effect of some anti-HIV drugs. This development could have occurred for several reasons, including the use of weak regimens, difficulty absorbing medicines, drug interactions or poor adherence (not taking a regimen exactly as directed). For instance, people who were treated with anti-HIV drugs in the late 1980s and early 1990s would usually have been prescribed and used single-agent therapy (monotherapy), initially with AZT and later with other similar chemically related drugs such as 3TC (lamivudine), ddI (didanosine, Videx), ddC (zalcitabine, Hivid) and d4T (stavudine, Zerit). These drugs are all nucleoside analogues (nukes). They are relatively weak when used by themselves, so people treated with one or two nukes alone tended to develop HIV that could resist these drugs. In those early years of the HIV pandemic, comparatively little was known about how best to use the relatively few drugs available.

A memory of resistance

Although more potent drugs (and combinations of potent drugs) became available after 1996, researchers found that if people had HIV that was resistant to one or more drugs in the past, such strains were still present but at relatively low proportions—even in people whose viral loads in the blood were undetectable. These strains were largely driven out of the blood and, according to researchers, “archived” deep within the body’s reservoir of HIV-infected cells, likely residing in the lymph nodes, lymphatic tissues and possibly the brain and reproductive tract. In experiments when people have started taking their old ART on which they previously experienced treatment failure, these archived, drug-resistant strains of HIV quickly emerge into the blood.

HIV in the body

Based on the results of complex studies of HIV in the lab that Mesplède and colleagues have done, and also the results of experiments with people (carried out by other research teams), Mesplède has developed a theory of what is happening with HIV in the body. He thinks that even in people whose viral load blood tests suggest that HIV is undetectable thanks to potent combination anti-HIV therapy (commonly called ART), HIV is still being produced in the lymph nodes and lymphatic tissues. These parts of the immune system harbour cells that serve as a reservoir for HIV.

The reservoir is an important idea in HIV research. Scientists are refining their methods for assessing the reservoir, or burden, of HIV-infected cells. Such methods will be an important part of efforts to cure HIV, as clinical trials are planned or underway in which researchers hope to shrink the size of the reservoir. If the size of the reservoir can be significantly reduced, then one day it might be possible, in theory, to cure HIV infection.

Focus on dolutegravir

Mesplède’s experiments in the lab, as well as interim results from some studies, support his idea that testing dolutegravir in people who have never previously used ART or who have never previously used integrase inhibitors may prove useful. Specifically, he hopes that dolutegravir-based regimens in those populations could, in theory, interfere with the production of HIV in the reservoir, perhaps even somewhat diminishing it.

Mesplède, Wainberg and colleagues have designed a clinical trial to try to find out the impact of integrase inhibitors on the reservoir of HIV-infected cells. The trial is code-named CTN 294 (and nicknamed LAHDGA) and will be sponsored by the CIHR HIV Clinical Trials Network; it will be observational in design. In this study, researchers hope to enroll 60 HIV-positive adults who are
already on ART and whose viral load is less than 50 copies/mL.

Participants taking the following specific regimens will be enrolled:

- dolutegravir-based regimen – 20 participants
- elvitegravir (in Genvoya and Stribild)-based regimen – 20 participants
- a regimen without integrase inhibitors – 20 people

This study should be viewed as a pilot to test an interesting idea. If Mesplède and colleagues find evidence to support their theory, a larger prospective clinical trial will be needed to confirm their results. Although the CTN has sponsored the LAHDGA study, Mesplède, Wainberg and colleagues still need to raise funds to conduct it.

Acknowledgement

We thank Thibault Mesplède, PhD, McGill University, for his expert review and research assistance.

REFERENCES:


E. A study from Barcelona about switching to dolutegravir monotherapy

Doctors in Barcelona, Spain, enrolled HIV-positive participants taking anti-HIV therapy whose viral load in the blood was less than 50 copies/mL. No participant had a history of resistance to integrase inhibitors. Due to the risky nature of the study—therapy with just one drug—researchers were careful to enroll only people who were generally having issues with their current regimen, such as the following, and who might need a simplified regimen:

- drug-related side effects
- other illnesses (co-morbidities) that were difficult to manage because of interactions between medicines
- HIV that was resistant to many therapies and resulted in doctors prescribing complex and burdensome regimens

Researchers reported results from 33 participants who were switched from some other therapy (in some cases monotherapy with darunavir [Prezista] + ritonavir [Norvir]). Overall, the results suggest that switching to dolutegravir monotherapy may be useful in some people, at least in the short term.

Study details

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

- age ~ 56 years
- 45% men, 55% women
• years since HIV diagnosis – 19
• history of AIDS-related infections/ complications – 39%
• CD4+ count – 600 cells/mm$^3$
• CD8+ count – 990 cells/mm$^3$
• HIV viral load – less than 37 copies/mL
• years with an undetectable viral load – 8

Results

After 24 weeks of dolutegravir monotherapy, 32 out of 33 participants (97%) maintained an undetectable viral load. There were no significant changes in cell counts.

In one participant, doctors detected what they called “low-level virological failure” after four weeks in the study. That is, his viral load was 88 copies/mL. Another viral load test was subsequently requested and doctors found that it had increased to 155 copies/mL. We will provide more information about this case later.

Changes in other blood tests

Overall, after 24 weeks of dolutegravir monotherapy, researchers found that most participants had significant and favourable decreases in the following fatty substances in their blood:

• triglycerides
• total cholesterol

Other changes

The study doctors reported that the following occurred once participants switched to dolutegravir monotherapy:

• no drug interactions between dolutegravir and medicines used to treat other conditions
• nausea, vomiting and/or diarrhea, which was a problem for some participants prior to the study, “improved or disappeared in nine of 11 [affected participants]”
• the risk of a heart attack declined
• one participant with kidney injury had improvement

Adverse events

No participant stopped taking dolutegravir due to side effects.

Two participants had serious adverse events, as follows:

• amputation of a foot due to complications stemming from diabetes
• syphilis

However, none of these adverse events were caused by dolutegravir.

Focus on one case

The doctors noted that the man in whom dolutegravir monotherapy failed had a complex medical history.

At the time of the study he was 52 years old and had been HIV positive for 12 years. During that time he had been on 10 different regimens. One of these regimens contained the integrase inhibitor raltegravir (Isentress). His raltegravir-based regimen had failed though technicians were unable to find any HIV with mutations or changes in its genes suggesting raltegravir resistance.

Although he had a history of using multiple street drugs, the man stated that for the past two years he had not used these drugs. During the past two years he had been treated with darunavir (Prezista) + low-dose ritonavir (Norvir). Since the purpose of low-dose ritonavir in such a regimen is to boost and maintain high levels of darunavir, his therapy can be described as darunavir monotherapy. During the time he took darunavir monotherapy, his viral load was less than 37 copies/mL, suggesting good adherence.

The man was also taking many other medicines, including the following:

• paliperidone (Invega Sustenna, Xeplion) – a long-acting drug used to treat bipolar disorder and schizophrenia
• trazodone – an antidepressant
• lorazepam (Ativan) – for management of anxiety
• losartan – to treat his higher-than-normal blood pressure
• pitavastatin (Livalo) – to help reduce his elevated cholesterol levels

When his viral load became detectable in the fourth week of the study, doctors advised him to
raise his dose of dolutegravir to 50 mg twice daily, but he refused.

At the 24th week of the study, his viral load was detectable at 101 copies/mL. However, using conventional tests on his blood samples, technicians were unable to find HIV that was resistant to integrase inhibitors. When the tests used only in research settings were applied, they found that about 7% of the HIV-infected cells in his samples had a moderate degree of resistance to dolutegravir.

Bear in mind

In this non-randomized pilot study, researchers found that some treatment-experienced participants did not experience obvious harm and may even benefit when switching to dolutegravir monotherapy. However, as mentioned previously, this study was not randomized, was relatively small and ran for a relatively short time. Furthermore, participants were carefully selected. Treatment failure in the study occurred in one participant who had previously used raltegravir (and who also experienced treatment failure when that drug was used). As raltegravir is chemically related to dolutegravir, HIV that is resistant to raltegravir can also have some degree of resistance to dolutegravir (and elvitegravir, found in Stribild and Genvoya).

It is still early days for dolutegravir monotherapy and much additional research is required.

REFERENCE:

F. A study from Paris about switching to dolutegravir monotherapy

Doctors in Paris conducted a study whereby participants whose current regimen resulted in an undetectable viral load in their blood (less than 50 copies/mL) could be switched to dolutegravir 50 mg once daily.

Between May 2014 and January 2015, 28 participants were recruited and had the following average profile at the start of the study:

- age – 48 years
- no data on gender were released
- years taking ART – 17
- years with a viral load less than 50 copies/mL – 7
- CD4+ cell count – 624 cells/mm³

During the first 24 weeks of the study, participants had blood drawn at regular intervals for extensive analysis.

Researchers presented 24 weeks of data and plan to continue to monitor participants.

Results

For the first 12 weeks of the study, all participants maintained a viral load less than 50 copies/mL. Furthermore, using a more sensitive test, researchers found that nearly all participants maintained a viral load less than 20 copies/mL up to the first 12 weeks. On or after that time point, three participants developed virological failure (details about this appear next). Investigating these cases and trying to find the cause of virological failure is important because trials are planned that seek to test simplified regimens containing dolutegravir.

Case 1

Prior to the present study, a 35-year-old woman had taken darunavir (Prezista) + low-dose ritonavir (Norvir) + Truvada (tenofovir + FTC). This had resulted in her viral load being less than 50 copies/mL. In the past she had used a combination of two drugs, etravirine (Integrase) + the integrase inhibitor raltegravir (Isentress). At the start of the present study her CD4+ count was 525 cells/mm³.

In the 12th week of the study her viral load became detectable, reaching 136 copies/mL. She continued taking dolutegravir monotherapy and by the 24th week of the study her viral load had climbed to 2,220 copies/mL.

The amount of dolutegravir in her blood throughout the study was usually within the expected range, suggesting good adherence. However, as seen by her viral load in week 24, HIV had developed a degree of resistance to all integrase inhibitors, including dolutegravir. Faced with her increasing viral load, doctors doubled her dose of
dolutegravir to 50 mg twice daily (the dose used to treat treatment-experienced patients) and added Truvada to her regimen. This reduced her viral load back to undetectable. Using a more sensitive test, her viral load was less than 20 copies/mL.

Case 2

This was a 56-year-old man who had taken different regimens for the past 18 years. For seven months prior to entering the present study, his regimen was Stribild, which contains the integrase inhibitor elvitegravir. His CD4+ count was 1,108 cells/mm³.

The man’s viral load while on dolutegravir monotherapy was less than 50 copies/mL and also less than 20 copies/mL when tested with an ultrasensitive assay. However, in the 12th week of the study, his viral load rose to 138 copies/mL. He remained on monotherapy and his viral load rose to 469 copies/mL in week 13. Analysis of his blood revealed that HIV had developed a moderate degree of resistance to raltegravir and elvitegravir, and therefore to dolutegravir as well.

Doctors changed his regimen, increasing his dose of dolutegravir to 50 mg twice daily and adding Truvada. This helped re-suppress his viral load to less than 20 copies/mL by the 24th week of the study.

Case 3

This involved a 57-year-old man who had been taking a combination of raltegravir + Truvada for six years prior to entering the study. During that time his viral load was generally less than 20 copies/mL. On one occasion it had risen to 37 copies/mL. His CD4+ count was 940 cells/mm³.

For most of the study this man’s viral load was less than 20 copies/mL but by the 24th week it had risen to 291 copies/mL. Analysis of his HIV revealed that it had developed resistance to raltegravir, elvitegravir and dolutegravir. Doctors then gave him a combination of rilpivirine (Edurant) + Truvada. Over the course of 10 subsequent weeks his viral load gradually declined, reaching 43 copies/mL by week 38.

Caution

The researchers warn that people who have had previous exposure to integrase inhibitors are not likely to be ideal candidates for dolutegravir monotherapy. This issue arises because the development of strains of HIV with the ability to partially resist integrase inhibitors can occur in some people who use these drugs. Initially at least, these strains may occur at relatively low levels. But when therapy is sub-optimal—that is, when one’s viral load is increasing while they are taking an integrase inhibitor—these strains can become more common and their ability to resist integrase inhibitors intensifies.

Overall, nearly 89% of participants were able to have their viral load stay at less than 20 copies/mL for the duration of the study. The research teams plans to monitor the participants for another six months.

Bear in mind that the Paris study was small and not randomized, so its findings are preliminary at best.

REFERENCE:


G. Dual therapy with dolutegravir + 3TC

Researchers in Argentina conducted a somewhat different experiment from the dolutegravir monotherapy clinical trials reported on earlier in this issue of TreatmentUpdate. They decided to use a simplified regimen of dolutegravir + 3TC (lamivudine) as the initial therapy for HIV infection. Compared to dolutegravir, 3TC is relatively weak. However, 3TC is generally well tolerated, would increase the antiviral effect of dolutegravir and is in widespread use in many countries as part of combination therapy for HIV.

For the study in Argentina (called Paddle), researchers recruited 20 participants who underwent frequent visits to the study’s laboratory so that their blood could be drawn for analysis. Researchers wanted an initially intensive level of monitoring, as they were concerned about the possibility that a dual regimen may not be
sufficiently powerful to significantly reduce and suppress viral load. In this report, we have the first 24-week results of Paddle; further results should be released later this year, as researchers continue the study for a total of 48 weeks. Researchers found that the combination of dolutegravir + 3TC was well tolerated and sufficiently effective in lowering viral loads.

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

- age – 34 years
- 19 men, one woman
- viral load – 24,000 copies/mL (about 4.4 logs)
- CD4+ count – 500 cells/mm³

**Results**
During the first two weeks of the study, viral load fell rapidly by about 2 logs. After this time it declined more slowly. By the second week of the study, 11 participants had their viral loads fall below the 50-copy/mL mark. However, by the fourth week of the study, 85% of participants (17 out of 20) had their viral loads fall below the 50-copy/mL mark. The remaining three participants had viral loads of 288, 67 and 64 copies/mL respectively. By the eighth week of the study, all participants had an undetectable viral load.

Participants’ CD4+ counts increased rapidly, reaching about 700 cells/mm³ at week 12 and stabilizing after that point.

**Side effects**
Nearly all reported side effects were of mild intensity, such as the following:

- feeling sleepy during the daytime – one person
- intestinal pain – one person
- headache – two people
- diarrhea – one person
- nausea – two people

The exception was a person who had a headache of moderate intensity.

These side effects occurred during the first week of the study and resolved shortly after.

Lab tests did not find any severely abnormal results.

**For the future**
Researchers plan to continue this pilot study to the 48th week. Although the results are promising, much more research needs to be conducted.

**REFERENCE:**

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**H. Dolutegravir and the fetus**
Potent combination anti-HIV therapy (commonly called ART) together with other measures has greatly reduced the risk of HIV-positive mothers giving birth to infected babies, particularly in high-income countries where care and treatment is widely available. By driving the amount of HIV in the mother down to very low levels, ART plays a key role in protecting the fetus from infection.

Anti-HIV drugs move from the mother’s circulation to that of the fetus via a physical connection during pregnancy called the placenta. It is therefore important to study the movement of these drugs across the placenta so that researchers can assess the potential of medicines to protect the fetus from HIV.

**Integrase inhibitors**
The most potent class of anti-HIV drugs is called integrase inhibitors. Examples of these drugs include the following:

- dolutegravir (Tivicay and in Triumeq)
- elvitegravir (in Genvoya and Stribild)
- raltegravir (Isentress)

When used as part of ART, integrase inhibitor-based regimens quickly reduce viral load. These drugs are generally well tolerated, and raltegravir and dolutegravir have relatively few interactions with other medicines. For both of these reasons
integrase inhibitor–based regimens, particularly those that include raltegravir, have been, in some cases, prescribed by doctors for pregnant women who have recently been diagnosed with HIV.

Enter dolutegravir

Dolutegravir is the newest integrase inhibitor and it is increasingly being prescribed in high-income countries. As some HIV-positive women who use dolutegravir-containing ART can become pregnant, it is important to begin to investigate how this drug can affect the fetus. To begin to explore this possibility, researchers in Nijmegen, the Netherlands, have developed a system in their lab, using donated placentas, to simulate the blood circulation between fetus and mother.

Key findings

Dolutegravir can cross the placenta and enter the blood supply of the fetus.

The concentration of dolutegravir in the fetus’ blood supply was considered “moderate to high” by the researchers. Based on their results, the Dutch researchers expect that in pregnant mothers who use dolutegravir-containing ART can become pregnant, it is important to begin to investigate how this drug can affect the fetus. To begin to explore this possibility, researchers in Nijmegen, the Netherlands, have developed a system in their lab, using donated placentas, to simulate the blood circulation between fetus and mother.

This relatively high concentration of dolutegravir in the circulation of the fetus means that it is likely that the drug can protect the fetus from HIV. However, the Dutch researchers also note that the high concentration of dolutegravir raises the potential issue of side effects for the fetus. In studies with pregnant mice and rats, other researchers have not found “direct evidence” that exposure to dolutegravir resulted in birth defects or affected the development of the fetus.

A need to report pregnancy outcomes

Most anti-HIV drugs are not formally tested in large randomized clinical trials of pregnant women. The vast majority of information about the safety of ART in pregnancy, both for the mother and fetus, comes from observational studies and databases that collect information on pregnancy in HIV-positive women. Therefore, the Dutch researchers strongly encourage doctors to continue to submit reports to databases on the results of pregnancy in HIV-positive pregnant women. Given that dolutegravir is a relatively new drug in the history of HIV treatment, this is particularly important.

REFERENCE:

I. Dolutegravir—Interaction with atazanavir during pregnancy

Doctors in France have reported the use of dolutegravir to intensify therapy in an HIV-positive pregnant woman. The baby was born prematurely and does not appear to be infected with HIV. However, it appears that the mother’s regimen raised and prolonged levels of dolutegravir in the infant. Fortunately, this did not seem to cause any injury to the baby.

The French doctors were monitoring an HIV-positive pregnant woman whose potent combination anti-HIV therapy (ART) worked until late in pregnancy. Her ART suddenly and unexpectedly began to fail, as her viral load became detectable in the 22nd week of her pregnancy (279 copies/mL) and became higher at the 32nd week of her pregnancy (453 copies/mL).

The woman’s regimen consisted of the following medications taken once daily:

- Truvada (tenofovir 300 mg and FTC 200 mg)
- atazanavir (Reyataz) 300 mg
- low-dose ritonavir (Norvir) 100 mg

Doctors and pharmacologists analysed the woman’s stored blood samples and found that levels of her regimen were within their expected range. This suggested that her ability to take medicines was not an issue. Next, technicians assessed the woman’s HIV for resistance to treatment. They found that the virus had become resistant to FTC (and likely to the related drug 3TC [lamivudine]) and possibly to tenofovir as well. Since having an undetectable viral load in the mother plays a key role in protecting the fetus from HIV, doctors decided to intensify her therapy with dolutegravir
50 mg once daily so that her entire regimen could continue on a once-daily schedule.

The baby was born prematurely at 37 weeks and delivered by C-section. At delivery the mother’s viral load was undetectable. Blood samples from the placenta did not detect any HIV-infected cells, suggesting the possibility that the fetus was not infected. However, the doctors prescribed intravenous AZT after birth as a precaution in case the infant had been exposed to HIV.

The French researchers also assessed the blood of the infant for dolutegravir. They found that shortly after birth and for the first nine days outside the womb, the infant had concentrations of dolutegravir that were high. Indeed, the concentration of the drug was what would be expected in adults. In contrast, shortly after birth, levels of the other drugs that the mother took during pregnancy were very low. By the 18th day after delivery, the concentration of dolutegravir in the infant’s blood was virtually absent.

The doctors suggest that the atazanavir taken by the mother probably delayed the breakdown and excretion of dolutegravir in both the mother and fetus (and later baby). Also, the enzymes in the baby that could break down dolutegravir were immature. Both of these factors likely contributed to the prolonged and elevated levels of dolutegravir in the infant. They noted that the increased exposure to dolutegravir by the infant did not seem to cause harm. The baby was born prematurely, but some analyses suggest an increased risk of premature birth in HIV-positive women regardless of the use of ART.

REFERENCES:

J. A successful pregnancy and birth outcome with dolutegravir-based ART

Doctors in Rome, Italy, recently reported the successful use of dolutegravir-based potent combination anti-HIV therapy (ART) to prevent HIV transmission from mother to child. There were no birth defects detected in the infant. Although these results are good, much more research analysing other pregnancies will be needed to determine the safety of dolutegravir in pregnancy.

Case details

A woman infected at birth had what her doctors described as “a long history of exposure to [anti-HIV therapy]” that began in her early childhood. Over the years her doctors found that she had “experienced many virological failures.” This led to strains of HIV in her body that had developed the ability to resist many drugs from all major classes. Such strains are called multidrug resistant (MDR).

In the 18 months before she became pregnant, the woman’s anti-HIV regimen was as follows:

- Truvada (tenofovir 300 mg and FTC 200 mg) one tablet daily
- darunavir (Prezista) 600 mg twice daily
- low-dose ritonavir (Norvir) 100 mg twice daily
- raltegravir (Isentress) 400 mg twice daily

Despite this regimen, blood tests in April 2013 revealed that her CD4+ count was 12 cells/mm³ and her viral load was 126,000 copies/mL. Resistance testing confirmed that she had MDR-HIV.

Doctors then replaced raltegravir with dolutegravir 50 mg twice daily (the dose used by treatment-experienced patients) and left the rest of her regimen unchanged. Subsequently her CD4+ count rose to 135 cells/mm³ and her viral load fell to less than 40 copies/mL.
In January 2014, the woman expressed a desire to become pregnant despite the concerns of her doctors, perhaps because the safety of dolutegravir in pregnancy was unknown. In March 2014 she became pregnant. At that time her CD4+ count was 262 cells/mm$^3$ and her viral load was again less than 40 copies/mL.

A comprehensive medical team at her local infectious disease clinic stated that they “exhaustively” counselled the woman and her partner about the risks of HIV transmission to the fetus and whether the use of dolutegravir should be interrupted or continued because of its unknown fetal safety. The woman and her partner chose to continue taking dolutegravir.

Tests and scans during pregnancy did not reveal any defects and the fetus developed normally. Shortly before the woman gave birth, blood tests found that her CD4+ count was almost 500 cells/mm$^3$ and her viral load was still less than 40 copies/mL.

In the 37th week of her pregnancy, the woman went into premature labour. Doctors therefore decided to deliver the baby via C-section. While the woman was in labour and delivery, nurses gave her intravenous AZT (zidovudine, Retrovir) as an additional measure to help reduce the risk of HIV transmission to her baby. After birth, the infant received a combination of the drugs AZT + 3TC for the first six weeks of life. This therapy for the baby is considered a form of post-exposure prophylaxis—it helps prevent infection taking hold in the baby should it have been exposed to HIV during the birthing process.

Tests that sought to detect HIV’s genetic material in the baby were negative at birth, one month after and six months after birth, showing that she was not infected.

Examination by doctors did not find any birth defects and the baby is healthy.

The doctors credited the woman’s excellent adherence to ART and her regular clinic visits to the effort made by the medical staff to nurture a good relationship with her. The Italian team encourages other doctors to “actively” involve HIV-positive women in decision-making around care and treatment during pregnancy. This advice is especially important because not all women can plan their pregnancies and receive pre-pregnancy counselling.

The report by the Italian doctors is a very positive one. However, readers should note that data from many HIV-positive pregnant women is needed before the safety of dolutegravir in pregnancy is known.

REFERENCE:
## 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. CATIE provides information resources to help people living with HIV and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature. CATIE endeavours to provide the most up-to-date and accurate information at the time of publication. However, information changes and users are encouraged to ensure they have the most current information. Users relying solely on this information do so entirely at their own risk. Neither CATIE nor any of its partners or funders, nor any of their employees, directors, officers or volunteers may be held liable for damages of any kind that may result from the use or misuse of any such information. Any opinions expressed herein or in any article or publication accessed or published or provided by CATIE may not reflect the policies or opinions of CATIE or any partners or funders.

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CATIE is Canada’s source for up-to-date, unbiased information about HIV and hepatitis C. We connect people living with HIV or hepatitis C, at-risk communities, healthcare providers and community organizations with the knowledge, resources and expertise to reduce transmission and improve quality of life. For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients’ needs. CATIE provides such information through a comprehensive website ([www.catie.ca](http://www.catie.ca)), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

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