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I ANTI-HIV AGENTS

A. Biktarvy begins to get listed on provincial drug formularies

Biktarvy is a pill containing the following three medicines:

- bictegravir (an integrase inhibitor)
- TAF (tenofovir alafenamide; the safer formulation of tenofovir)
- FTC (emtricitabine)

In clinical trials, Biktarvy was as effective as standard triple treatment with a leading integrase inhibitor, dolutegravir. Biktarvy is generally well tolerated.

Biktarvy was approved in Canada about a year ago and its manufacturer, Gilead Sciences, has been engaged in negotiation with Canada's provinces and territories about the cost of this drug. Subsequently, some provinces have added Biktarvy to their list of subsidized medicines (this list is commonly called a formulary). As this issue of *TreatmentUpdate* went to press, the following provinces had added Biktarvy to their formularies:

- Alberta
- Ontario
- Quebec
- Saskatchewan

In the coming months, other provinces/territories will hopefully add Biktarvy to their formularies.

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B. Dovato (dolutegravir + 3TC) in initial HIV treatment

In late August 2019, a pill called Dovato (containing dolutegravir + 3TC) was approved for the treatment of HIV in Canada and other high-income countries. The approval of Dovato was based on data from a clinical trial called Gemini conducted by Dovato manufacturer ViiV Healthcare.

Gemini is ongoing and aims to study the effectiveness of starting HIV treatment with a combination of two drugs: the integrase inhibitor dolutegravir and the nucleoside analogue 3TC. Results after one year found that the two-drug regimen was similarly effective to standard three-drug therapy. The detailed two-year results from Gemini reveal that dolutegravir + 3TC continues to show similar effectiveness and safety as standard three-drug therapy.

Study details

For Gemini, doctors and nurses recruited HIV-positive people who had never previously used HIV treatment (ART) from countries in North and South America, Europe, South Africa and Taiwan.

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

- age – 32 years
- 85% men, 15% women
- major ethno-racial groups: white – 68%; black – 13%; Asian – 10%
- viral load – 32,000 copies/mL (about 20% of participants had a viral load greater than 100,000 copies/mL)
- CD4+ count – 433 cells/mm^3 (about 9% of participants had CD4+ count of 200 cells/mm^3 or lower)
- no participants had hepatitis B virus infection
- no participants had HIV with the ability to significantly resist drugs such as 3TC, FTC (emtricitabine) or protease inhibitors

Participants were randomly assigned to receive one of the following regimens:

- dolutegravir + 3TC (dolutegravir dual therapy)
- dolutegravir + tenofovir DF + FTC (dolutegravir triple therapy)

The trial was double blind; that is, neither participants nor most of the study team knew which participant received which combination. This masking of the study medicines continued to the 96th week of the study.

Results—viral load

The proportions of participants who achieved and maintained an undetectable viral load (less than 50 copies/mL) were as follows:

Week 48
- dolutegravir dual therapy – 86% (616 of 716 participants)
- dolutegravir triple therapy – 90% (642 of 717 participants)

These differences in viral load at week 48 were not statistically significant. The regimen of two drugs was considered to be roughly equivalent to the regimen of three drugs. The technical term for this is "non-inferior."

The proportions of participants with a viral load of 50 copies/mL or higher were distributed as follows:

- dolutegravir dual therapy – 3%
- dolutegravir triple therapy – 2%

Participants with no virological data available were distributed as follows:

- dolutegravir dual therapy – 11%
- dolutegravir triple therapy – 9%

(Note that percentages do not total 100% due to rounding.)

The main reasons that participants did not have virological data available was due to withdrawal from the study due to side effects, distributed as follows:

- dolutegravir dual therapy – 3%
- dolutegravir triple therapy – 3%

Some participants discontinued the study for other reasons, such as loss of contact with the clinic, failure to follow study procedures, withdrawal by a physician, or withdrawal based on personal reasons. The distribution of these participants was as follows:

- dolutegravir dual therapy – 8%
- dolutegravir triple therapy – 5%

One person who was taking dolutegravir triple therapy left the study prematurely because their regimen wasn't working.

Viral loads and CD4+ cell counts

Researchers assessed the response to treatment based on participants' viral loads or CD4+ cell counts upon entering the study. Here are their analyses:

Viral load of 100,000 copies/mL or less
- dolutegravir dual therapy – 87% achieved an undetectable viral load at week 96
- dolutegravir triple therapy – 90% achieved an undetectable viral load at week 96

Viral load greater than 100,000 copies/mL
- dolutegravir dual therapy – 84% achieved an undetectable viral load at week 96
- dolutegravir triple therapy – 86% achieved an undetectable viral load at week 96

CD4+ count greater than 200 cells/mm^3
- dolutegravir dual therapy – 88% achieved an undetectable viral load at week 96
- dolutegravir triple therapy – 90% achieved an undetectable viral load at week 96

CD4+ count of 200 or less cells/mm^3
- dolutegravir dual therapy – 68% achieved an undetectable viral load at week 96
- dolutegravir triple therapy – 87% achieved an undetectable viral load at week 96

Although there were not large numbers of people in the last subgroup, dolutegravir + 3TC appeared at first glance to be less powerful among people who had low CD4+ cell counts. However, this difference in the proportions of participants with an undetectable viral load at week 96 was driven by people dropping out of the study for many different reasons, not because of virological failure. When the lack of virological failure is taken into account, there was no major difference in outcome between dual and triple treatment in people who entered the study with low CD4+ cell counts.

Side effects and complications

In general, there was a low risk for side effects and complications in the study. The overall proportions of participants who experienced a side effect of at least moderate intensity were distributed as follows:

- dolutegravir dual therapy – 7%
- dolutegravir triple therapy – 8%

Premature departure from the study

The proportions of overall participants who experienced a side effect that led to premature departure from the study were distributed as follows:

- dolutegravir dual therapy – 3%
- dolutegravir triple therapy – 3%

Other reasons for premature withdrawal from the study were as follows:

Neuro-psychiatric issues
- dolutegravir dual therapy – 1%
- dolutegravir triple therapy – 1%

Kidney-related issues
- dolutegravir dual therapy – less than 1%
- dolutegravir triple therapy – 1%

Severe thinning of bones (osteoporosis)
- dolutegravir dual therapy – 0%
- dolutegravir triple therapy – less than 1%

Weight gain
- dolutegravir dual therapy – 1.8%
- dolutegravir triple therapy – 1.4%

Three participants died from the following causes:

- heart attack
- Burkitt's lymphoma
- coronary artery disease

All three of these participants were taking dolutegravir dual therapy. However, investigation revealed that the study drugs did not play a role in their deaths.

Focus on kidney and bone health

Overall, participants who took dolutegravir dual therapy had significantly better kidney health results than people who took dolutegravir triple therapy. This difference largely arose because triple therapy included tenofovir DF (TDF). This formulation of tenofovir is associated with kidney injury in some people. The results also showed that the combination of dolutegravir + 3TC is generally safe for the kidneys.

Similar trends were seen in assessments of bone health based on blood tests for certain proteins and peptides.

Lipids—cholesterol and triglycerides

Overall, changes in lipid levels were very modest and favoured the dual-drug regimen.

Overall

The 96-week findings from Gemini confirm the beneficial effects of a powerful dual-drug regimen based on dolutegravir. Importantly, no participant developed HIV that was resistant to the study medicines.

Both study regimens were generally safe but dolutegravir dual therapy was better tolerated and had favourable effects on bone and kidney health.

For the future

As mentioned earlier, a pill called Dovato (containing dolutegravir + 3TC) has been approved for the treatment of HIV in Canada. In the autumn, the leading HIV treatment guidelines produced under the aegis of the U.S. Department of Health and Human Services (DHHS) will assess the data on Dovato and consider its place in recommendations for the use of initial HIV treatment; that is, whether it is a preferred or alternative regimen for the initial treatment of HIV.

REFERENCE:

Cahn P, Madero JS, Arribas J, et al. Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naïve adults with HIV-1 infection – 96-week results from the GEMINI studies. In: Proceedings and abstracts of the *10th IAS Conference on Science*, 21–24 July 2019. Mexico City, Mexico. Abstract WEAB0404LB.

C. Switching to Dovato (dolutegravir + 3TC) from a TAF-based regimen

The dual-drug regimen dolutegravir + 3TC, sold in a pill called Dovato, has been approved in Canada and other high-income countries for the treatment of HIV infection. This regimen is anchored by the power of dolutegravir, a potent integrase inhibitor.

Dovato may therefore be considered for use by doctors in two ways:

- intitial HIV treatment
- simplification (explained below)

Some people on standard triple- or four-drug therapy whose viral load has been stably suppressed could be considered for switching to a simpler two-drug regimen of Dovato. Such people should not have pre-existing resistance to dolutegravir or 3TC, have hepatitis B virus co-infection or prior instances of virological failure.

Doctors increasingly expect that many people who take HIV treatment (ART) will have a near-normal life expectancy. Given this tremendous benefit of ART, it makes sense to consider how many medicines people are taking and for how long, at least in people who are highly adherent and whose viral loads are suppressed. A study in Southern Alberta (link: https://www.catie.ca/en/catienews/2018-08-23/alberta-clinic-explores-long-term-survival-among-hiv-positive-people) found that some patients had been taking kilograms of ART over several decades. The long-term benefits of ART are clear—survival and generally good health. However, what is less clear is whether there are drawbacks to taking ART over many decades. This concept will probably be debated among doctors and scientists in the years ahead. Later in this issue of *TreatmentUpdate* we discuss several issues that may be relevant to the use of dolutegravir-based dual therapy.

A phase III clinical trial called Tango is underway. This study has enrolled participants taking a standard regimen that includes TAF (tenofovir alafenamide), some of whom were switched to a reduced drug regimen of two medicines—dolutegravir + 3TC.

After 48 weeks of being on dolutegravir and 3TC, researchers found similar rates of effectiveness among the regimens. There was no development of resistance to dolutegravir or 3TC. Furthermore, the dual-drug regimen was generally safe.

Study details

Participants had a suppressed viral load on their pre-study regimen for at least six months and all such regimens included TAF.

Participants did not have the following:

- hepatitis B virus co-infection
- prior instances of virological failure
- resistance to integrase inhibitors or nucleoside analogues

Participants were randomly assigned to be on one of the following regimens:

- switch to dolutegravir + 3TC
- continue taking a TAF-based regimen

The average profile of participants upon study entry was as follows:

- age – 40 years
- 92% men, 8% women
- major ethno-racial groups: white – 80%; black – 15%; Asian – 4%
- CD4+ count – 700 cells/mm^3

Pre-study regimens

The distribution of participants' pre-study regimens was as follows:

- 80% were taking Genvoya, a fixed-dose regimen of elvitegravir, cobicistat, TAF and FTC
- 12% were taking Odefsey, a fixed-dose combination of rilpivirine, TAF and FTC
- 8% were taking darunavir (Prezista) with ritonavir or cobicistat and TAF and FTC

Tango is expected to continue for about four years.

Results

The proportions of participants with an undetectable viral load (less than 50 copies/mL) at week 48 were as follows:

- dolutegravir dual therapy – 93% (344 of 369 people)
- TAF-based regimen – 93% (346 of 372 people)

The study was designed to assess the non-inferiority of dolutegravir dual therapy against TAF-based regimens (usually containing three or four anti-HIV drugs). Statistically, the study found that both study regimens were similarly effective. That is, dolutegravir dual therapy was not worse than and not better than TAF-based regimens.

Side effects and complications

During clinical trials, a range of unfortunate events can occur. These events could be caused by the study drugs, the underlying disease process or issues outside of the clinical trial. Researchers refer to all of these unfortunate events as "adverse events." The overall distribution of adverse events during the study was as follows:

- dolutegravir dual therapy – 80%
- TAF-based regimen – 79%

However, the distribution of adverse events of at least moderate intensity that were drug side effects were distributed as follows:

- dolutegravir dual therapy – 6% (17 of 295 people)
- TAF-based regimen – 1% (three of 292 people)

Examples of drug side effects that occurred in more than 0.5% of participants were as follows:

Problems with sleep
- dolutegravir dual therapy – 1%
- TAF-based regimen – 0%

Constipation
- dolutegravir dual therapy – 1%
- TAF-based regimen – 0%

Flatulence
- dolutegravir dual therapy – 1%
- TAF-based regimen – 0%

Headache
- dolutegravir dual therapy – 1%
- TAF-based regimen – 0%

The proportions of participants who left the study prematurely because of side effects were distributed as follows:

- dolutegravir dual therapy – 2%
- TAF-based regimen – less than 1%

Weight

At week 48, participants on both study regimens had gained about 1 kg of weight (about 2.2 lbs)—this was listed as a possible general adverse effect. However, increased weight was reported as a drug-related side effect in three people (1%) who used dolutegravir dual therapy and in six people (2%) who continued to use a TAF-based regimen.

Premature withdrawal from the study

People on both regimens left the study prematurely because of different adverse events. Note that in the cases below, which occurred in people who were using dolutegravir dual therapy, some people experienced more than one adverse event, which caused them to leave. In some cases, investigation was able to assess the cause of the problem:

- anxiety – 3 cases
- sleep problems – 3 cases
- increased weight – 2 cases
- lack of energy – 2 cases
- abdominal discomfort – 1 case
- heart burn – 1 case
- nausea – 1 case
- numbness and tingling in the mouth – 1 case
- drug hypersensitivity – 1 case
- gunshot wound – 1 case; this was unrelated to the study medicines
- lymphoma – 1 case; this was not caused by study medicines
- lung cancer – 1 case; this was not caused by study medicines
- problems concentrating – 1 case
- prickling, decreased sense of touch – 1 case
- irritability – 1 case
- thoughts of suicide – 1 case; this was not caused by the study medicines
- loss of sensation in the genitals – 1 case
- tingling, numbness in the genitals – 1 case
- itchy skin – 1 case

Many of the cases above were not likely linked to the study medicines. They are more likely to have been related to an underlying disease process or, in some cases, other, non-HIV-related medicines that participants were taking.

Premature departure from the study among TAF users

Note that in the cases below, some people experienced more than one adverse event, which caused them to leave the study. In some cases, investigation was able to assess the cause of the problem:

- weight gain – 1 person
- depression – 1 person
- attempted suicide – 1 person; this was unrelated to the study drug

Focus on lipids, kidneys and bones

Overall, regardless of the study regimen, many participants had generally acceptable or good levels of the following in their blood or urine samples:

- lipids (cholesterol, triglycerides)
- markers of bone health
- markers of kidney health

A note on archived virus

Prior to entering the study, some people may have been infected with a strain of HIV that is partially or wholly resistant to drugs such as 3TC, FTC or TAF. Drug resistance can also arise when people do not adhere to their medicines. As HIV in the blood is suppressed by the use of potent regimens, infected cells with HIV that might be resistant to 3TC and FTC are not actively producing virus and are either circulating in the blood at low levels or lie deep within lymph nodes and lymphoid tissues. In the setting of a suppressed viral load, virologists say that HIV-infected cells that have the ability to partially resist treatment are "archived" somewhere in the body. This archived (and drug-resistant strain of) HIV can emerge from hiding and spread in the body if doses are skipped or missed.

In people whose viral loads are suppressed by powerful drugs such as dolutegravir dual treatment, does archived drug resistant HIV matter? To explore this issue, researchers with Tango analysed stored blood samples and found small numbers of infected cells with the ability to resist 3TC and/or FTC. HIV that has the ability to resist these drugs carries mutations in its genome called M184V and/or M184I. The distribution of people with these mutations at the start of the study was as follows:

- dolutegravir dual therapy – 4 people (about 1%)
- TAF-based regimen – 3 people (about 1%)

At week 48, all seven of these people had a viral load that was less than 50 copies/mL.

Among participants who did not have archived mutations associated with resistance to 3TC and/or FTC at the start of the study, the proportions with a suppressed viral load at week 48 were as follows:

- dolutegravir dual therapy – 100%
- TAF-based regimen – 99%

The lower figure among TAF users occurred because two people had a viral load greater than 50 copies/mL at the end of the study. However, the M184V/M184I mutation did not have an impact on treatment success in the study.

Bear in mind

Most people in Tango did not have archived mutations to 3TC; those who did were generally screened out of the study (only about 1% of people in Tango had such mutations). However, the analysis of mutations and viral load in the study is reassuring about the potency of dolutegravir + 3TC when used in the context of switching regimens among people who are virologically suppressed (having a viral load less than 50 copies/mL). Another trial called Salsa is planned. In this study, scientists will assess the effectiveness of dolutegravir + 3TC in switching patients from different regimens.

REFERENCE:

van Wyk J, Ajana F, Bisshop F, et al. Switching to DTG+3TC fixed dose combination (FDC) is non-inferior to continuing a TAF-based regimen (TBR) in maintaining virologic suppression through 24 weeks (TANGO Study). In: Proceedings and abstracts of the *10th IAS Conference on Science*, 21–24 July 2019. Mexico City, Mexico. Abstract WEAB0403LB.

D. Some issues to consider with Dovato (dolutegravir + 3TC)

The clinical trials for Dovato (a combination of dolutegravir and 3TC) for the initial treatment of HIV or for a change to a simpler regimen have found this dual-drug therapy as effective as standard triple-drug therapy.

Dovato has been approved by regulatory authorities in North America and the European Union for use as HIV therapy. Since 1996, treatment guidelines in North America have only recommended regimens containing three (or, in some cases, four) drugs for HIV treatment. In thecontext of initial HIV treatment, the use of Dovato is unusual and perhaps revolutionary. Note that Dovato's use comes with caveats that we will mention later.

Guidelines

When treating people with HIV, physicians and nurses rely on the largest and most comprehensive HIV treatment guidelines produced under the aegis of the U.S. Department of Health and Human Services (DHHS). People in the field of HIV treatment commonly call this document the DHHS guidelines. These guidelines will be updated sometime in the autumn of 2019 and will list the place of Dovato in HIV treatment—indicating whether or not it is a preferred regimen for the initial treatment of HIV infection.

Starting treatment, past experiments

Other dual regimens that have been studied in the past—used either for the initiation of HIV treatment (ART) or for reducing the number of drugs (simplification)—have not produced high and relatively fast rates of virological suppression as dolutegravir + 3TC did. Or, if they did, such suppression did not last and such studies were relatively small compared to Gemini. Some early studies that attempted to use a reduced number of drugs for initial ART or after achievement of viral suppression with a more complex regimen included some of the following drugs:

- indinavir (Crixivan)
- ritonavir + lopinavir (in Kaletra)
- ritonavir + atazanavir; atazanavir + 3TC
- ritonavir + darunavir

What is different with this regimen is that Dovato contains dolutegravir, an integrase inhibitor with powerful anti-HIV activity. Yet, despite the very good results seen in clinical trials of dolutegravir + 3TC, doctors and their patients have to sometimes deal with more than two decades of received wisdom from clinical trials in which dual regimens were not successful. It may not be easy to break through this psychological barrier, at least initially.

The importance of the CD4+ cell count

Gemini contained a relatively small proportion of people with a CD4+ count of 200 or less cells. Such people usually have issues affecting absorption (intestinal inflammation, diarrhea) because of underlying HIV-related injury to the intestines and/or other infections and usually require three anti-HIV drugs. Although Dovato performed well in this sub-group of participants, some doctors may wish to see more data from clinical trials in people with less than 200 CD4+ cells/mm^3 before prescribing it in this population.

Viral load at baseline

In Gemini, the proportions of participants who entered the study with a viral load greater than 100,000 copies/mL and who subsequently achieved and maintained a suppressed viral load at week 48 were distributed as follows:

- dolutegravir dual therapy – 92% (129 of 140 people)
- dolutegravir triple therapy – 90% (135 of 153 people)

By week 96, the proportions of people who entered the study with a high viral load and who still maintained a suppressed viral load were distributed as follows:

- dolutegravir dual therapy – 84% maintained an undetectable viral load
- dolutegravir triple therapy – 86% maintained an undetectable viral load

Analyses of clinical trials of dolutegravir + 3TC (Dovato)—such as Gemini, done by Dovato manufacturer ViiV Healthcare, and a smaller study by the American AIDS Clinical Trials Group (ACTG)—have shown that people who initiate treatment with dolutegravir + 3TC seem to do well as long as their initial viral load is not greater than 500,000 copies/mL. Whether this gives doctors the confidence to initiate dolutegravir dual treatment in patients with viral loads that are high (less than but close to 500,000 copies/mL) remains to be seen.

Good adherence is critical for long-term success

For some people, taking ART as one pill a day for many years is not a problem; it is easily integrated into their lives. For other people, perhaps those who have chaotic lives and have difficulty taking medication because of struggles with other issues, it is not clear if dolutegravir dual therapy is the best option. People who have difficulty with adherence are not usually enrolled in large pivotal studies of ART.

If resistance to dolutegravir + 3TC develops because of poor adherence, the consequences could be serious, particularly for people who are heavily treatment experienced. HIV that is resistant to dolutegravir and 3TC will probably also be resistant to other integrase inhibitors such as bictegravir (in Biktarvy), elvitegravir (in Genvoya), raltegravir and the experimental integrase inhibitor cabotegravir. HIV that is resistant to one drug in a class can become resistant to other members of that class—this is called cross-resistance.

If a person is resistant to 3TC, they are also likely resistant to FTC, which is in many regimens. Thus, people who have resistance to dolutegravir + 3TC will have limited treatment options and their doctors will have to cobble together regimens using older, less tolerable drugs, likely with twice-daily schedules.

For people with chaotic lives or who have difficulty taking a pill on a daily basis, long-acting ART, which is likely to be approved in high-income countries by mid-2020, might be a useful option. However, people with resistance to integrase inhibitors and nucleoside analogues (3TC, FTC and so on) will likely not be able to use the first generation of long-acting treatment due to cross-resistance.

Pre-existing resistance

ViiV Healthcare recommends that dolutegravir + 3TC not be used by people who have HIV that is resistant to these medicines.

Co-infection with hepatitis B virus (HBV)

HBV co-infection occurs among some people with HIV. Having 3TC as the only drug in a regimen with anti-HBV activity is likely not an optimal approach to treatment for co-infected people. A regimen containing a combination of drugs that are active against both HIV and HBV—such as TDF + FTC or TAF (tenofovir alafenamide, the safer form of tenofovir) + FTC—is likely better at suppressing HBV and keeping it suppressed.

Does U=U apply to dolutegravir dual regimens?

Standard triple treatment usually consists of two nucleoside analogues anchored by a powerful drug, such as the following:

- an integrase inhibitor
- a boosted protease inhibitor (for example darunavir + a small dose of ritonavir)
- a non-nuke (such as efavirenz or rilpivirine)

These standard regimens have been used in well-designed clinical trials to assess the potential for the sexual transmission of HIV. In these clinical trials, once participants achieved a suppressed viral load and maintained the suppressed viral load by continuing to take ART exactly as directed, scientists found that HIV was not spread to their sexual partners. This finding led to the expression "undetectable equals untransmittable"—meaning that people who have undetectable HIV in the blood do not spread HIV to their sexual partners. This idea has been popularized as "U=U." However, what about dolutegravir dual regimens? Can they support U=U and also suppress HIV in the blood and genital fluids?

Scientists in the U.S. sought to explore this issue by assessing data from a sub-group of people in clinical trials of dolutegravir + 3TC vs. standard triple therapy. The scientists focused on two groups of people as follows:

- Group 1: 38 people—18 who switched to dolutegravir + 3TC from a standard triple-drug regimen and 20 who remained on triple-drug therapy
- Group 2: 13 people whose initial ART was dolutegravir + 3TC

Among the 51 people were 45 men and six women. Researchers analysed a total of 76 semen samples collected at different points in time over 48 weeks. They also collected 12 swabs of vaginal fluid over the same period.

Results

The scientists found that three men and no women had detectable (more than 40 copies/mL) viral loads. The cases of these three men were as follows:

- The first case was one of 20 men taking triple-drug therapy (rilpivirine + TDF + FTC), with a viral load in his blood of 179 copies and a semen HIV viral load of 42 copies/mL, both at week 48. This person had missed doses of his medicine in the past two weeks.
- In the second case, a man had been taking dolutegravir + 3TC with very low viral loads in his blood—less than 20 copies/mL at week 36 and 31 copies/mL at week 48. The viral load in his semen at week 36 was 488 copies/mL and 79 copies/mL at week 48. He did not miss any doses of ART (it is not clear how adherence was assessed in this sub-study).
- In the third case, another man was taking dolutegravir + 3TC and routinely had a suppressed viral load (less than 40 copies/mL). At week 24 he had a viral load in his semen of 48 copies/mL. His adherence was good.

The scientists did not detect any chlamydia or gonorrhoea. Sexually transmitted infections (STIs) in the genital tract could cause localized inflammation and increase HIV replication there. However, larger studies have found that even HIV-positive people with STIs who have a suppressed viral load in their blood from ART do not spread HIV to sexual partners.

As viral loads were generally low in both blood and semen, it was difficult to analyse HIV for the presence of virus that had developed the ability to resist ART. In the case of one man whose semen viral load was 488 copies (case two), technicians did not find any drug-resistant HIV.

Note that from time to time, even on standard triple therapy, it is possible that a very small proportion of people can occasionally have low but detectable levels of HIV in their genital fluids even when the amount of virus in their blood is suppressed. These low levels of HIV in the genital fluid are not

sufficient to cause infection in a partner as long as the person with HIV continues to take ART exactly as prescribed and directed and their viral load in the blood is suppressed.

Putting it all together

The U.S. scientists reviewed their results and made the following statement:

> "In our pilot study of 51 adults living with HIV, the frequency of genital HIV shedding while virologically suppressed in the blood was similar between those who were on standard 3-drug ART and those were who on dolutegravir + 3TC as initial or maintenance therapy. The frequency of genital [HIV] shedding fell within the lower end of the range reported for 3-drug regimens in other studies (2% to 20%)…. Taken together, these results suggest that dolutegravir + 3TC is effective in controlling genital HIV shedding, which accounts for most HIV transmission."

Furthermore, the U.S. scientists also stated:

> "In conclusion, in this small pilot study, we did not detect concerning signals about the efficacy of the 2-drug regimen of dolutegravir + 3TC in controlling genital HIV RNA shedding, hence prevention of viral transmission when HIV RNA is undetectable in blood plasma. These preliminary results suggest that dolutegravir + 3TC likely confers similar transmission prevention benefits as triple therapy."

HIV and the brain

HIV-infected cells can enter the brain and spinal cord—the central nervous system (CNS). Once in those locations, infected cells can release viral proteins that affect brain cells and their ability to function. Dolutegravir and 3TC penetrate the CNS, which bodes well for maintaining brain health among people with HIV. However, when doctors are dealing with suspected or confirmed cases of HIV-related brain injury, more complex regimens are likely required and they are extremely unlikely to prescribe only a combination of dolutegravir and 3TC.

The long-term effects of HIV and ART

ART helps to restore the immune system to the point where the risk of AIDS-related complications (serious infections and certain cancers) is virtually zero among the vast majority of ART users whose viral load is suppressed and who have a robust increase in CD4+ cell counts.

Yet, despite excellent adherence and suppressed viral loads over the long term, scientists have found that subtle immunological defects persist. Small amounts of HIV are found in samples from deep within the body, in some lymph nodes and organs of the immune system such as the spleen, brain, and so on. Persistent HIV infection, even in ART users, is associated with higher-than-normal levels of inflammation and immune activation. It is possible that over the long term this inflammation and immune activation could degrade the immune system. What's more, as people grow older, their immune system's effectiveness gradually wanes. Taken together, these issues—the combination of an aging immune system and subtly impaired immunity—do not mean that AIDS will (re)appear. Rather, the accumulation of subtle immunological defects could increase the *risk* for cancer in some HIV-positive people.

Some scientists theorize that taking ART for decades could in some way contribute to a small degree of harm to susceptible tissues or parts of cells. However, this is a theory. Given the massive survival advantage conferred by ART (with many people having near-normal life expectancy), this benefit easily outweighs any theoretical disadvantage, particularly when modern drugs are used.

Some doctors may decide, for whatever reason(s), to decrease the amount of anti-HIV medication taken from three to two drugs in patients with the following profile:

- the absence of HIV with any resistance to treatment
- a history of very good adherence
- no hepatitis B virus co-infection

In such patients, Dovato (dolutegravir + 3TC) and Juluca (dolutegravir + rilpivirine) could be options to consider.

In high-income countries

Today in Canada and many high-income countries, regimens for first- and second-line use are highly effective and generally well tolerated. This situation is likely to continue for the foreseeable future. There will always be a small proportion of people who have issues with one or more drugs for the following reasons:

- genetics – this can make a person more susceptible to a hypersensitivity reaction to a new or old anti-HIV drug
- complex underlying conditions – some people have liver or kidney injury and so their doctor must devise a carefully tailored regimen to reduce the risk of toxicity to injured organs
- initiating ART when the immune system is severely weakened – people who do this are more susceptible to inflammatory syndromes and drug side effects until their immune system becomes stronger

However, for now, there is no evidence that recommended first-line regimens in 2019 cause a harmful and clinically significant degree of impact on the health and well-being of the vast majority of people with HIV who take them.

Aging

HIV-positive people will take multiple medicines over the course of their lives because they are living longer. Such additional medicines could include those to manage the following conditions:

- abnormal cholesterol levels
- anxiety or depression
- arthritis
- excessive formation of blood clots
- higher-than-normal blood pressure
- problems with sleep
- problems breathing
- substance dependency

In this context, if doctors have an opportunity to safely reduce the burden of medicines, then perhaps a simplified regimen such as Dovato (or Juluca) could be considered in carefully selected patients.

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E. More dual HIV regimens are coming

The pharmaceutical company ViiV Healthcare has been the leader in developing potent dual-drug HIV regimens, such as the following:

- Juluca – a pill containing dolutegravir + rilpivirine; this is meant to be taken once daily for maintenance therapy. That is, a person whose viral load has been stably suppressed on standard triple therapy can be considered for a switch to Juluca. As they are already virologically suppressed, it is not surprising that clinical trials have shown that Juluca continues to suppress HIV.
- Dovato – a pill containing dolutegravir + 3TC; this is meant to be taken once daily either as initial or maintenance treatment for HIV.

ViiV is also developing a long-acting injectable regimen. This is how it works: First, patients are initiated on standard oral treatment that suppresses their viral load. After several months of oral treatment and the achievement of a suppressed viral load (less than 50 copies/mL), and provided no sustained or serious side effects occur, they can be switched to injectable treatment, likely given every two months. Injectable treatment consists of two drugs: cabotegravir and rilpivirine. Clinical trials have shown that such injectable treatment is well tolerated and works at suppressing HIV.

Other companies will test dual regimens

Another pharmaceutical company, Merck, is also entering the dual-regimen field. Merck plans to test a combination of a non-nuke called doravirine with a new drug called islatravir (formerly MK-8591) in people new to HIV treatment as well as a form of switch therapy in people who are using standard triple therapy. We will have more information about islatravir in the future.

Another leader in the field of HIV treatment and prevention is Gilead Sciences. It is said that Gilead plans to consider testing a dual-drug regimen. Details are not available at this time.

In the early 1990s, HIV treatment for some people consisted of dual-drug regimens, such as AZT + 3TC or AZT + ddI. Such regimens based on nucleoside analogues did not confer benefit for long and were toxic. Today, dual therapy has returned, with more powerful and safer therapies anchored by integrase inhibitors and possibly other classes of drugs in the future.

The next decade holds the promise of dual therapy for both initiating ART and as maintenance/switch therapy in virally suppressed patients.

F. Decreasing the risk of neural tube defects with dolutegravir

Dolutegravir belongs to a class of anti-HIV drugs called integrase inhibitors. In Canada and other high-income countries, dolutegravir is sold in the following formulations and under the following brand names:

- Tivicay – dolutegravir
- Dovato – dolutegravir + 3TC
- Juluca – dolutegravir + rilpivirine
- Triumeq – dolutegravir + 3TC + abacavir

An earlier alert from Botswana

Since about 2014, the Southern African country of Botswana has been collecting data on the outcome of pregnancies of HIV-positive women. The main purpose of the data collection was to be sure that the anti-HIV drug efavirenz (Sustiva and in Atripla) was safe for the fetus when it was taken at conception.

In 2016 Botswana began a shift from the use of efavirenz-based regimens for initial HIV treatment to dolutegravir-based ART. As a result, data began to accumulate about the safety of dolutegravir taken at conception or later in pregnancy.

Based on this data, researchers in Botswana found "a potential early signal" for a type of birth defect called neural tube defects. This potential early signal was associated with four infants born to a group of 426 HIV-positive mothers who had been taking dolutegravir at the time of conception.

Subsequently, the World Health Organization (WHO) and regulatory agencies in Canada and other countries issued cautionary statements and guidance about the use of dolutegravir in women who were taking it and who might become pregnant or who were pregnant.

It is important to bear in mind that scientists in Botswana found "a potential early signal." This cautionary statement and the guidance subsequently issued were intended to reduce the possibility of harm to the fetus until further data were collected and analysed. Note that animal studies prior to the licensure of dolutegravir did not find any association with an increased risk for neural tube defects.

An updated analysis

The Botswana scientists have reviewed health-related information on 119,033 infants born to HIV-positive mothers between August 15, 2014 and March 31, 2019. A total of 98 neural tube defects occurred (0.08% of births). The distribution of these neural tube defects by medication use at the time of conception was as follows:

- dolutegravir-based ART – 0.30% (five neural tube defects in 1,683 infants)
- all non-dolutegravir-based ART – 0.10% (15 neural tube defects in 14,792 infants)
- efavirenz-based ART – 0.04% (three neural tube defects in 7,959 infants)

Among the nearly 90,000 infants born to HIV-negative mothers during the study, 70 had neural tube defects (0.08%).

All but one of the birth defects associated with dolutegravir occurred prior to May 2018. This is important to note because it was in that month that the scientists became aware of the potential link between dolutegravir taken at conception and neural tube defects.

Between May 2018 and March 2019, one additional neural tube defect was found in an infant born to a mother who used dolutegravir at conception. This resulted in a proportion of 0.08% (one out of 1,257 infants).

Trends

According to Rebecca Zash, MD, who presented the findings from Botswana, dolutegravir-associated neural tube defects began to fall during the study. The initial association of dolutegravir with potential birth defects was unexpected. The subsequent decrease in the rate of neural tube defects during the study was equally unexpected and occurred before the WHO and regulatory agencies released their cautionary statements and guidance. Furthermore, Dr. Zash and colleagues have stated that the number of births "among women who were taking dolutegravir at conception continued to rise after May 2018…"

Why was there a potential association?

Scientists, regulatory agencies and ViiV Healthcare, the manufacturer of dolutegravir, never expected a potentially increased risk of birth defects of any kind associated with the use of dolutegravir at conception. As a result, they are not certain as to why the risk of neural tube defects appeared in the first place and why this risk is now decreasing in Botswana. Also, the risk has only been reported in Botswana, but not in Brazil, Cameroon or South Africa or in Canada, France or other high-income countries. Arguably, documented exposures to dolutegravir during pregnancy and monitoring for the possibility of birth defects in infants has only been done in studies in those other countries where the number of pregnant users of dolutegravir has been relatively small compared to Botswana.

There are at least two theories for the potential signal between dolutegravir and neural tube defects as advanced by scientists in Botswana:

- Low levels of the B-complex vitamin folate (the synthetic form of this is called folic acid) in the diet of women. Deficiency of folate has long been linked to increased risk of neural tube defects in studies with HIV-negative pregnant women outside of Botswana. To reduce this risk, some countries fortify flour with folic acid. Botswana does not. It is plausible that in some women high levels of dolutegravir could have occurred at the time of conception, perhaps interfering with the fetus' access to folate and subsequently increasing the risk for birth defects. However, at this time, there is no firm evidence for this theory.

- Some women in Botswana may have genes that increase the risk for neural tube defects in the presence of dolutegravir during conception. Again, there is no firm evidence for this.

Bear in mind

The Botswana study was observational in design. Such studies cannot prove "cause and effect"; that is, they cannot prove that dolutegravir caused neural tube defects. The Botswana scientists took into account potential factors that could have had an impact on the risk of neural tube defects, specifically the following:

- diabetes
- use of anti-seizure drugs
- use of the antibiotic Bactrim/Septra (trimethoprim-sulfamethoxazole)
- obesity

However, none of these were present in mothers who used dolutegravir at conception and gave birth to infants with birth defects.

In context

The scientists in Botswana made the following statement about their findings:

> "The data…suggest a potential association between dolutegravir exposure at conception and the development of neural tube defects. Although the prevalence of neural tube defects was three times as high with dolutegravir as with non-dolutegravir [ART], this represented only approximately two defects per 1,000 [births]."

Infectious disease specialists Diane Havlir, MD, and Meg Doherty, MD, have stated in an editorial in the *New England Journal of Medicine* that the data on dolutegravir from Botswana should not "preclude its use among women of reproductive age." However, they also stated that more data are needed, specifically that "large-scale pharmacosurveillance studies of birth outcomes in more countries are the only way to get an answer to the actual risk of neural tube defects and other adverse birth outcomes."

The data from Botswana also show that efavirenz used at the time of conception is not linked to an increased risk of birth defects. Efavirenz-based regimens were once widely used in high-income countries. However, use of efavirenz has been linked to an increased risk for neuro-psychiatric side effects, and, in a small proportion of people (about 1%), an increased risk for thoughts about suicide and attempted suicide.

In Canada and other high-income countries, the next step is for regulatory agencies to issue any updates to their guidance originally issued in 2018 concerning the use of dolutegravir at conception and in pregnancy. In the absence of such guidance, doctors will likely continue to use regimens for which they have experience in pregnant HIV-positive women—such as ritonavir-boosted darunavir or the older twice-daily formulation of raltegravir (Isentress). Such regimens have not been linked to an increased risk for neural tube defects.

Resource

CATIE News: Agencies issue caution about use of dolutegravir by pregnant HIV-positive women

(www.catie.ca/en/catienews/2018-05-24/agencies-issue-caution-about-use-dolutegravir-pregnant-hiv-positive-women)

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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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