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## Contents

### I ANTI-HIV AGENTS

A. The re-emergence of dual therapy	1
B. Dolutegravir + rilpivirine as maintenance therapy	3
C. Dolutegravir + 3TC as maintenance therapy—a pilot study	6
D. Preliminary results of dolutegravir + 3TC for initial therapy of HIV	7
E. Who tends to gain weight with HIV treatment?	8

### I ANTI-HIV AGENTS

#### A. The re-emergence of dual therapy

In the past decade, attempts have been made in clinical trials to simplify combination HIV therapy (ART) from a standard mix of three active drugs to two or even one-drug maintenance therapy. The idea is that after using a standard number of drugs to initiate and suppress HIV levels to less than 50 copies/mL, therapy can be reduced to fewer drugs to maintain viral suppression. Most such simplification studies have had issues.

The pharmaceutical company ViiV Healthcare has been developing a simplified therapy with the following drugs taken orally:

- dolutegravir (Tivicay and in Triumeq)
- rilpivirine (Edurant and in Complera and Odefsey)

Dolutegravir is a potent integrase inhibitor and rilpivirine is a non-nuke. The combination of both drugs in one pill has been licensed in the U.S. and sold under the brand name Juluca. The U.S. Food and Drug Administration (FDA) has stated that dolutegravir-rilpivirine can replace a patient's current regimen as long as their viral load is undetectable (less than 50 copies/mL) and they have been "on a stable regimen for at least six months with no history of treatment failure and no known [mutations in their HIV] associated with resistance to [dolutegravir and rilpivirine]."

Dolutegravir-rilpivirine will likely be licensed in Canada and the European Union in the spring of 2018.

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## Swords

The clinical trials that provided the data to support licensure of dolutegravir-rilpivirine are called Sword-1 and Sword-2. They showed that the combination of dolutegravir-rilpivirine is highly effective and generally safe. Furthermore, there was no increase in levels of inflammation in participants who switched from standard ART to dolutegravir-rilpivirine. This is important because HIV causes heightened inflammation that researchers suspect can accelerate injury to many organ-systems. This inflammation is partially reduced with standard ART and it is reassuring that it remains at reduced levels with dolutegravir-rilpivirine.

## Changes over time

The approval of dolutegravir-rilpivirine by the FDA represents a major change in what constitutes a regimen for maintaining the effects of HIV treatment. Prior to 1996, standard therapy consisted of one and then a combination of two drugs, usually nukes (nucleoside analogues). At best, these conferred temporary benefit, as nukes are relatively weak when taken on their own. Furthermore, the nukes in widespread use at that time were relatively toxic. However, in 1996 several pivotal trials showed that a combination of three drugs from two classes, usually a protease inhibitor and two nukes, generally resulted in dramatic and sustained improvements in health and survival. Subsequently, other classes of drugs—non-nukes and integrase inhibitors—became widely used but they too were combined with nukes. Combinations that include integrase inhibitors have been shown to be the most powerful against HIV. Integrase inhibitor-based combinations reduce viral loads quickly, tend to have the fewest interactions with other medicines and are usually well tolerated. Such combinations are recommended by leading treatment guidelines for the initial therapy of HIV.

## Why consider dual therapy?

Researchers estimate that about 50% of HIV-positive people in North America and Western Europe are at least 50 years old. As HIV-positive people age, they are likely to need multiple medicines to treat emerging health conditions, such as higher-than-normal blood pressure, abnormal lipid levels, pre-diabetes and diabetes, anxiety and depression, osteoporosis, and so on. Some researchers and doctors, particularly geriatric specialists, are

concerned that the burden of so many medicines over time has the potential to adversely affect the body and a person's health. They think there may be potential for reducing the total number of medicines a person takes, including, in some cases, HIV medicines. In particular, some doctors think that it is possible that some patients may benefit from reduced exposure to nukes.

## Overcoming a legacy of the past

Most clinical trials of simplified therapy have been imperfect. They have tended to be small, did not collect a wide range of data, had combinations that may not be as potent as those available today, or, if promising results were initially shown, they were not confirmed in another study. This has all changed with the development of a single pill containing dolutegravir-rilpivirine, which has been tested in two large randomized clinical trials. Both drugs complement each other and interfere with the production of copies of HIV by infected cells in different ways.

There are still other issues to consider about dolutegravir-rilpivirine, such as the following:

### Reservoir

What effect will this combination have on the pool (called the “reservoir” by researchers) of HIV-infected cells that is deep within parts of the body, such as the lymph nodes and lymphatic tissues, the brain, the bone marrow, the spleen? To be fair, under standard ART, this pool is maintained. However, studies are needed to compare the size of the reservoir in people taking dolutegravir-rilpivirine against people taking standard ART.

### Brain

What impact will there be on neurocognitive function? Both dolutegravir and rilpivirine can penetrate the cerebrospinal fluid (CSF), which surrounds the brain and spinal cord, in quantities that can suppress HIV. So, it is very likely that relatively high concentrations of these drugs enter the brain. This is important because HIV-infected cells of the immune system can travel to and reside in the brain.

### Safety

In clinical trials, the combination was generally safe and well tolerated, though there was a small proportion of participants taking dolutegravir-rilpivirine who had neuropsychiatric problems—

sleep difficulties, anxiety and depression. This has been seen in other clinical trials of dolutegravir. It is likely that, in the future, doctors who have patients with these pre-existing problems will steer them toward other combinations.

### More to come

The combination of oral dolutegravir-rilpivirine in one pill taken once daily with food represents the first of several powerful dual regimens that are being developed as simplified maintenance therapy. Clinical trials are underway with long-acting injectable formulations of the experimental integrase inhibitor cabotegravir and rilpivirine. Smaller studies have also occurred with another combination—dolutegravir + 3TC (lamivudine). In this issue of *TreatmentUpdate* we review clinical trials of dual therapy with dolutegravir and another drug, mostly as maintenance therapy but also as initial therapy.

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1. Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet*. 2018; *in press*.
2. Boyd MA, Cooper DA. Combination ART: are two drugs as good as three? *Lancet*. 2018; *in press*.
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## B. Dolutegravir + rilpivirine as maintenance therapy

In two large randomized studies, called Sword-1 and Sword-2, researchers assigned more than 1,000 HIV-positive participants who were taking ART and who had an undetectable viral load to receive one of the following regimens:

- dolutegravir 50 mg + rilpivirine 25 mg (both drugs with a meal)
- continued use of their current ART regimen (CAR)

After 48 weeks, 95% of participants in both regimens had a viral load that was less than 50 copies/mL. Statistically, this demonstrates that dolutegravir-

rilpivirine was no worse than (the technical term for this is *non-inferior*) standard ART when used as maintenance therapy. Most side effects reported by participants taking dolutegravir-rilpivirine were mild and the combination was generally safe.

The combination of dolutegravir-rilpivirine will be co-formulated into one pill and will likely be approved in Canada and the European Union later this year and sold under the brand name Juluca.

### Study details

People recruited for this study were on their first or second combination, did not have a detectable viral load in the past six months, and did not have HIV that was significantly resistant to the main classes of commonly used treatments (nukes, non-nukes, protease inhibitors, integrase inhibitors). They also had never changed their initial regimen because of virological failure. According to the researchers, no one “at substantial risk of suicide” was allowed to participate and no one with hepatitis B virus co-infection was allowed into the study, as neither dolutegravir or rilpivirine have any activity against this virus.

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

- age – 43 years
- 78% men; 22% women
- major ethno-racial groups: white – 80%; black – 8%; Asian – 9%; Indigenous – 3%
- CD4+ cell count – 600 cells/mm<sup>3</sup>
- viral load – less than 50 copies/mL

Prior to randomization, commonly used regimens included the following:

- efavirenz + Truvada (TDF + FTC)
- raltegravir (Isentress) + Truvada
- darunavir (Prezista) + ritonavir + Truvada

The week 48 results were recently published.

### Results

As participants entered the study with viral loads already suppressed, researchers were interested in how many continued to remain suppressed by

the 48th week of the study. The proportions were as follows:

- dolutegravir-rilpivirine – 95%
- CAR – 95%

Statistically, this shows that dolutegravir-rilpivirine was no worse than, or non-inferior to, standard ART.

The actual proportions of participants who did not achieve virological suppression were low—about 1% of people on both regimens. The remaining 4% of participants on each regimen did not appear in the final analysis of viral loads at week 48 because they had withdrawn from the study for a variety of reasons.

Increases in CD4+ cell counts were modest and distributed as follows:

- dolutegravir-rilpivirine – an increase of 28 cells/mm<sup>3</sup>
- CAR – an increase of 22 cells/mm<sup>3</sup>

### Safety

Overall, researchers found that more drug-related adverse events were reported by participants taking dolutegravir-rilpivirine than standard ART. They were distributed as follows:

#### Headache

- dolutegravir-rilpivirine – 2% of participants
- CAR – zero participants

#### Diarrhea

- dolutegravir-rilpivirine – 2% of participants
- CAR – less than 1% of participants

### Focus on the mind

The researchers said that “most neuropsychiatric events” reported in the study were of mild-to-moderate intensity. Furthermore, they did not consider the majority of such events to be related to dolutegravir-rilpivirine or CAR. They said that neuropsychiatric events “often occurred in participants with a history of anxiety, depression or insomnia.”

Here is the overall distribution of psychiatric disorders that occurred in the study. According

to the researchers, these were *not* related to the study medicines:

- dolutegravir-rilpivirine – 12%
- CAR – 6%

The reason that such disorders were doubled in participants receiving dolutegravir-rilpivirine is unclear and was not explained by researchers. That the rate of these disorders was 6% among people who took CAR suggests that such problems are relatively common. This should not be surprising, as other studies have found higher rates of mental health issues among HIV-positive people.

In contrast to the previous distribution, here is the distribution of common neuropsychiatric problems that researchers determined were related to the study medicines:

#### Sleeping problems

- dolutegravir-rilpivirine – 3% of participants
- CAR – 2% of participants

#### Anxiety

- dolutegravir-rilpivirine – 2% of participants
- CAR – 2% of participants

#### Depression

- dolutegravir-rilpivirine – 3% of participants
- CAR – 1% of participants

#### Abnormal dreams

- dolutegravir-rilpivirine – 1% of participants
- CAR – zero participants

The number of people who left the study prematurely due to bothersome neuropsychiatric problems was distributed as follows:

- dolutegravir-rilpivirine – seven people
- CAR – one person

Thus, around 1% of participants left the study prematurely because of these problems when they were taking dolutegravir-rilpivirine.

One person taking dolutegravir-rilpivirine had thoughts of suicide and one person on CAR attempted suicide.

Both dolutegravir and rilpivirine can penetrate into the brain. On one hand, this is good because HIV-infected cells of the immune system travel to the



brain and some of them, particularly macrophages and related-cells, spend an extended period of time there. On the other hand, if high concentrations of these drugs accumulate in the brain, there is the potential for side effects in some people. The researchers said that the rate of neuropsychiatric side effects in the present study was similar to that seen in other studies of dolutegravir. They therefore do not think that rilpivirine caused additional neuropsychiatric side effects when used with dolutegravir. There will be more information on mental health issues and dolutegravir later in this report.

### Lab tests

#### Inflammation and dolutegravir-rilpivirine

HIV infection causes elevated levels of inflammation; this is partially reduced by ART. However, the level of inflammation in ART users never falls to the very low levels seen in healthy HIV-negative people. According to the study researchers, “there was no consistent pattern of change” when it came to assessments of proteins associated with inflammation, such as IL-6 (interleukin-6) and C-reactive protein (CRP). Overall, this suggests that inflammation levels in participants were stable.

#### Lipids and sugar

Dolutegravir-rilpivirine had no significant effect on fasting lipid levels—total cholesterol, levels of bad (LDL-C) and good cholesterol (HDL-C), cholesterol ratios and triglycerides.

There was a very small increase in fasting blood sugar levels among participants who took CAR vs. dolutegravir-rilpivirine.

#### Satisfaction and adherence

Researchers surveyed participants at different points in the study about their satisfaction with their regimens. They found that bothersome symptoms decreased significantly over time among participants taking dolutegravir-rilpivirine vs. symptoms associated with CAR.

Participants reported generally high rates of adherence to their regimens, around 98%.

### Bear in mind

The data from Sword-1 and Sword-2 show that the combination of dolutegravir-rilpivirine will likely find a role as maintenance therapy for some, perhaps many, HIV-positive people.

### Notes on mental health

Dolutegravir-rilpivirine will not be for everyone. For instance, the researchers said that they screened out potential participants at “substantial” risk for suicide from entering Sword-1 and Sword-2. Note that a small proportion of participants (1%) left the study due to neuropsychiatric effects of dolutegravir-rilpivirine, usually problems related to sleep, anxiety and/or depression. The researchers said that problems related to sleep, anxiety and/or depression “often” occurred in people with a history of such problems when they took dolutegravir-rilpivirine. Their use of the word “often” suggests that some people in this clinical trial who developed neuropsychiatric problems while on dolutegravir-rilpivirine did not have a history of such problems. Precisely why these problems occurred is not clear and requires further research. Other studies have found relatively high rates of mental health issues among people with HIV infection regardless of the type of medicines used.

Clinical trials of all medicines usually enroll participants who are relatively healthy compared to people with the same conditions in the community. Once dolutegravir-rilpivirine gets approved and subsidized by public and private insurance formularies, it is likely that a somewhat different profile of people in the community will receive these drugs compared to those in Sword-1 and Sword-2. As a result, the rates of side effects reported in the community may be greater than what was reported in clinical trials. A rough estimate for HIV drug development is that the rate of bothersome side effects will likely be about two- or three-fold greater in the average person in the community than what was reported in pivotal clinical trials. This has been the case with reports of neuropsychological side effects associated with dolutegravir compared to results from the pivotal clinical trials that were used for the approval of this drug. Thus, between 2% and possibly up to 6% of people who use dolutegravir-rilpivirine in the community may experience problems related to sleep, anxiety and/or depression possibly caused by dolutegravir-rilpivirine.

The good news is: Based on this rough estimate, it is likely that among the vast majority of people who use dolutegravir or dolutegravir-rilpivirine such side effects should not occur.

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1. Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet*. 2018; *in press*.
2. Boyd MA, Cooper DA. Combination ART: are two drugs as good as three? *Lancet*. 2018; *in press*.

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### C. Dolutegravir + 3TC as maintenance therapy—a pilot study

Dolutegravir (Tivicay and in Triumeq) is a powerful integrase inhibitor and is being tested in simplified regimens—consisting of two drugs—to maintain viral suppression in people who have previously used combinations containing three anti-HIV drugs.

Researchers in the U.S. conducted a randomized 48-week pilot study (called Aspire) of dolutegravir + the nuke (nucleoside analogue) 3TC vs. current ART regimen (CAR) in people who had achieved a viral load less than 50 copies/mL. The combination of dolutegravir-3TC was found to be similarly effective as standard three-drug ART. Larger studies to better assess the effectiveness and safety of dolutegravir-3TC as maintenance therapy are planned.

#### Study details

Researchers assessed data from 89 participants randomly assigned to dolutegravir-3TC (44 people) or CAR (45 people). Their average profile upon entering the study was as follows:

- age – 47 years
- 88% men, 12% women
- CD4+ count – 680 cells/mm<sup>3</sup>

Participants did not have the following:

- a history of virological failure after being on their previous regimens for more than one year

- HIV that was resistant to 3TC or other nukes or integrase inhibitors
- hepatitis B virus (HBV) co-infection

#### Results

Rates of virological success—that is, the proportions of participants who continued to have a suppressed (less than 50 copies/mL) viral load at week 24—were distributed as follows:

- dolutegravir-3TC – 93%
- CAR – 91%

Rates of viral suppression at week 48 were distributed as follows:

- dolutegravir-3TC – 91%
- CAR – 89%

Overall, 92% of participants disclosed that they had perfect adherence.

Increases in CD4+ cell counts were as follows:

- dolutegravir-3TC – 38 cells/mm<sup>3</sup>
- CAR – 28 cells/mm<sup>3</sup>

#### Other results

In general, participants who received dolutegravir-3TC had minimal changes to lipids (cholesterol, triglycerides) and measures of kidney health.

Severely abnormal lab tests were distributed as follows:

- dolutegravir-3TC – four people; two cases of higher-than-normal blood sugar, one case of abnormal bad cholesterol (LDL-C) and one case of elevated liver enzymes (ALT)
- CAR – three people; all had elevated levels of the waste product bilirubin in their blood

Due to the small size of the study, it is not possible to say if the lab test abnormalities reported among participants taking dolutegravir-3TC were caused by those drugs.

There were no neuropsychiatric symptoms reported by participants on either study regimen.

## Bear in mind

In this randomized study, the use of dolutegravir-3TC as maintenance therapy was similar in effectiveness and safety to standard ART. However, the study is small and not definitive. The results of this study provide a rationale for the larger studies that are planned to better understand the effects of dolutegravir-3TC.

## REFERENCE:

Taiwo BO, Zheng L, Stefanescu A, et al. ACTG A5353: A pilot study of dolutegravir plus lamivudine for initial treatment of HIV-1-infected participants with HIV-1 RNA < 500,000 copies/mL. *Clinical Infectious Diseases*. 2018; *in press*.

## D. Preliminary results of dolutegravir + 3TC for initial therapy of HIV

Dolutegravir (Tivicay and in Triumeq) is a powerful integrase inhibitor that is used by many HIV-positive people as part of combination HIV therapy (ART). 3TC (lamivudine) is a nuke (nucleoside analogue) that has been used for two decades and is generally safe and well tolerated.

Researchers in the U.S. with the AIDS Clinical Trials Group (ACTG) conducted a pilot study to gain some preliminary understanding of the potential for dolutegravir-3TC as an initial therapy for HIV.

Researchers recruited 120 participants who had not previously been exposed to treatment and gave them the following combination:

- dolutegravir 50 mg + 3TC 300 mg, both once daily

At the 24th week of the study, 90% of participants had a viral load less than 50 copies/mL. One person whose treatment failed developed HIV that was resistant to both dolutegravir and 3TC. The results from this study should be considered preliminary, as the study is expected to continue for a total of 52 weeks.

Large clinical trials are underway to compare the effectiveness and safety of dolutegravir-3TC vs. dolutegravir + TDF + FTC.

## Study details

Researchers recruited adults who had not previously taken ART, whose viral load was less than 500,000 copies and who did not have HIV with resistance to major classes of treatment (nukes, non-nukes, protease inhibitors, integrase inhibitors). Also, none of the participants were co-infected with hepatitis B virus (HBV).

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

- age – 30 years
- 87% men, 13% women
- CD4+ count – 387 cells/mm<sup>3</sup>
- viral load – 41,000 copies/mL  
(High viral loads: Note that 19% of participants had a viral load between 100,000 and 200,000 copies/mL and 12% had a viral load greater than 200,000 copies/mL but less than 500,000 copies/mL)

## Results

Overall, at week 24, 90% of participants had an undetectable viral load. When researchers sorted participants by their pre-study viral loads, the proportions with viral suppression at week 24 were as follows:

- participants with an initial viral load greater than 100,000 copies/mL – 89% had a suppressed viral load at week 24
- participants with an initial viral load of 100,000 copies/mL or less – 90% had a suppressed viral load at week 24

Seven participants left the study and/or stopped taking dolutegravir-3TC before week 24 for the following reasons:

- moved – two people
- imprisonment – one person
- lost contact with clinic – one person
- became pregnant – one person
- unable to take study drugs exactly as directed – one person
- unable to visit the study clinic – one person

At week 24, five participants had detectable viral loads. Here are more details about them:

- Two participants had detectable viral loads prior to week 24, one of whom entered the study with a viral load greater than 100,000 copies/mL. At week 24 their viral loads were between 50 and 200 copies/mL; by the study's design their viral loads were not high enough to be considered virological failure. The researchers referred to those two detectable viral loads as “non-success.”
- Three other participants had virological failure prior to week 24, one of whom entered the study with a viral load greater than 100,000 copies/mL. One participant repeatedly missed taking doses of the study medicines and quit the study at week 18. This participant developed resistance to 3TC and some integrase inhibitors. Researchers found that blood samples from all three participants had very low levels of dolutegravir, suggesting that they were not taking the drug.

At week 24, CD4+ cell counts increased by about 167 cells/mm<sup>3</sup>.

Ninety percent of participants disclosed perfect adherence.

### Safety

Two people developed serious adverse effects that were possibly related to the study medicines, as follows:

- severe kidney dysfunction
- sometimes, a racing heart beat when at rest

No neuropsychiatric side effects were reported.

None of the participants left the study because of side effects.

### Bear in mind

The study results should be considered preliminary. Further results will be made available in the future, as the study is expected to continue for 52 weeks. Larger trials of dolutegravir-3TC are planned or underway.

### REFERENCE:

Taiwo BO, Marconi VC, Berzins B, et al. Dolutegravir plus lamivudine maintain HIV-1 suppression through week 48 in a pilot randomized trial. *Clinical Infectious Diseases*. 2018; *in press*.

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### E. Who tends to gain weight with HIV treatment?

There has been a signal from two studies that suggest the possibility of weight gain among people who have used the integrase inhibitor dolutegravir (Tivicay and in Triumeq). However, those studies were done by looking back on data captured for another purpose. Such retrospective studies are useful for exploring an idea but firm conclusions cannot be drawn from them. That is why their results are only suggestive. Results from retrospective studies can be used to develop studies of a more robust statistical design.

To better explore the issue of weight gain among people using combination HIV therapy (ART), researchers at clinics in Milan and elsewhere in Italy conducted a large observational study, assessing health-related data drawn from more than 1,000 HIV-positive people. Participants in this study used different regimens, anchored by integrase inhibitors, protease inhibitors or non-nukes. The researchers found that participants taking common combinations of HIV drugs (not limited to integrase inhibitors) had increases in weight and body mass index (BMI, a relative measure of fatness or thinness). People who were most likely to gain weight were those who were relatively thin or older prior to starting therapy.

The Italian researchers attempted to adjust for factors that could have inadvertently biased their results and their findings are an important step up from retrospective studies. Still, observational studies, no matter how large, can never be used to draw firm conclusions, as they cannot prove cause and effect. There are several randomized, controlled studies of dolutegravir-based combinations underway. Once these studies are complete, the data can be analysed to assess trends in BMI and likely provide robust conclusions about the issue of weight gain and specific combinations of drugs.



## Study details

The Italian researchers used data from a project called SCOLTA and focused on the following groups of people on certain regimens:

755 ART-experienced participants who were taking regimens with the following integrase inhibitors:

- dolutegravir – 225 people
- raltegravir (Isentress) – 382 people
- elvitegravir (in Genvoya and Stribild) – 148 people

For purposes of comparison, the researchers collected and analysed data from 145 additional participants who were taking a regimen based on the protease inhibitor darunavir (Prezista and in PrezcoBix) and 218 others who were on a rilpivirine-based (Edurant and in Complera and Odefsey) regimen. Thus, there were a total of 1,118 participants in this study.

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

- age – 46 years
- 71% men, 29% women
- 19% had a CD4+ count below the 200 cell/mm<sup>3</sup> mark
- 40% had a detectable viral load
- BMI is an imperfect assessment but it is relatively simple to calculate as it is based on a person's weight and height. Participants fell into the following BMI categories: 6% were underweight, as they had a BMI less than 18.5; 61% were normal weight, as they had a BMI between 18.5 and 24.9; 27% were overweight, as they had a BMI between 25 and 29.9; and, 7% were obese, as their BMI was greater than 30.

Participants were monitored for at least one year.

## Results

Among all participants, BMI increased slightly by 0.19 six months after starting their current regimen and then by a total of 0.25 one year after starting their regimen. This suggests a modest increase in weight.

To account for factors that could have had an impact on weight gain, researchers performed

further analyses. Again, all regimens were associated with modest weight gain (an increase in BMI). Furthermore, there were no differences in BMI changes between participants taking a regimen anchored by an integrase inhibitor and participants who took regimens based on the protease inhibitors darunavir or rilpivirine.

Instead, researchers found an association between having the following factors at the start of the study and subsequent increase in weight:

- older age
- low BMI

## Why might weight gain increase with ART?

Prior to the widespread release of ART in high-income countries in 1996, some people with HIV experienced inadvertent weight loss that in some cases could become severe. This was commonly called the wasting syndrome. When analyses were done, researchers found that affected people tended to lose muscle mass.

The causes of weight loss in untreated HIV infection are complex and may be related to intestinal inflammation and injury from infections, altered metabolism, decreased levels of hormones such as testosterone, and loss of appetite.

Once ART became available in 1996, researchers reported increased weight in patients, particularly those who had been suffering from the wasting syndrome, though this increased weight was mostly due to fat rather than muscle. Given the improved health that accompanies the use of ART, it is natural to expect some degree of weight gain over time.

## Different studies

The researchers who designed the two retrospective studies that captured a signal of weight gain with dolutegravir were attempting to explore an idea to see if there was a possible trend. The next step has been done by the Italian researchers in SCOLTA, a study of an observational design. Such studies are good at finding associations but cannot prove “cause and effect”—that is, observational studies cannot prove that the use of integrase inhibitor-based regimens caused an increase in BMI.

More robust conclusions about weight gain can come from randomized, controlled studies, and several of these have been done and are underway or planned with dolutegravir-containing regimens. However, there is a possible issue with these studies. These randomized, controlled studies are meant to collect data for the licensure of dolutegravir-containing combinations. As such, participants will be young, relatively healthy people with HIV. Their findings may not be applicable to people in the community who are older and/or who have other health conditions.

### Bear in mind

There are many issues that can play a role in weight gain. Some of them are listed below:

- psychological and emotional – sometimes anxiety and even depression can cause people to eat more food and not have the energy to exercise; eating disorders
- physical – injuries; osteo-arthritis affecting the joints; low back pain; not enough exercise
- poor dietary habits
- sleeping problems
- biomedical – some cases of pre-diabetes and diabetes; abnormal levels of thyroid hormones; some medicines
- aging – a general trend is that as people age they tend to gain weight

These and other factors need to be taken into account when trying to assess the impact of medicines on weight and BMI. There is much work that lies ahead to be certain about the impact of dolutegravir on weight. But, for now, the results from the Italian study suggest that a modest increase in weight can occur in people taking commonly used regimens, whether or not these regimens include integrase inhibitors.

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### 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.

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### What CATIE Does

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.

### CATIE Publications

#### *TreatmentUpdate*

CATIE's flagship treatment digest on cutting-edge developments in HIV/AIDS and hepatitis C research and treatment. Subscribe to *TreatmentUpdate* and automatically receive an email notifying you the moment a new issue is available online or contact us at 1.800.263.1638 to receive a print subscription.

#### *CATIE News*

CATIE's bite-sized HIV and hepatitis C news bulletins.

#### *HepCInfo Updates*

CATIE's bi-weekly electronic newsletter highlighting key hepatitis C prevention, treatment and epidemiology information.

#### *A Practical Guide to HIV Drug Side Effects*

The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

#### *The Positive Side magazine*

Holistic health information and views written by and for people living with HIV.

#### *Fact Sheets*

Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

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