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### I COMPLICATIONS AND SIDE EFFECTS

#### A. From wasting to obesity—the changing issue of weight in HIV

In the early 1980s, medical records indicated that a new syndrome had suddenly and simultaneously appeared mostly among gay and bisexual men in North America and Western Europe, and among heterosexual people in parts of Central and East Africa. In parts of East Africa, people coined the name “slim” or “slim disease” to describe the effect of the new syndrome. It was initially associated with severe and relentless weight loss, fever, persistent oral yeast infections and sometimes other low-level but persistent infections.

Eventually severe, life-threatening infections would develop. By 1983, scientists at the Pasteur Institute in Paris had isolated a virus, now called HIV, that would eventually be linked to the cause of the syndrome seen around the world in different populations. In the early years of the AIDS pandemic, the wasting associated with the syndrome could become life threatening.

Today, thanks to the widespread availability of HIV testing and treatment (ART) in Canada and other high-income countries, AIDS-related conditions, including wasting, are now rare compared to the time before ART was available.

In the 21st century, weight continues to be an issue among HIV-positive people in high-income countries but in a different way than it was in the 1980s and early 1990s. Today there are increasing

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concerns among doctors and scientists that more HIV-positive people are becoming overweight or obese.

It should be noted that compared to earlier decades, more HIV-negative people have become overweight or obese.

Carrying excess weight has long-term implications for HIV-negative people, including an increased risk for pre-diabetes and diabetes, abnormal cholesterol levels and higher-than-normal blood pressure—all of which add to the risk of heart attack and stroke.

### The larger society

It is not clear why obesity is a growing problem among HIV-negative people than in the past. Scientists suspect that at least several factors may contribute to a risk for excessive weight including the following:

- insufficient exercise
- less access to healthy food and/or eating more processed food
- eating large portions of food
- taking certain prescribed medicines

It is plausible that there may also be environmental factors, such as chemical contaminants in food that may play a role in weight gain.

### Back to HIV

When people with HIV initiate ART, over the course of the first year or two they usually experience an increase in weight. Weight gain, particularly in people who were thin or underweight, is normal and signals a return to health. However, when the increased weight contributes to being overweight or obese, this can pave the way for health problems.

### Different treatments, different effects

#### Protease inhibitors

At the dawn of effective HIV treatment in 1996 and for many years after, regimens that came into use were anchored by a class of drugs called protease inhibitors. Over time, one protease inhibitor would be replaced by a more effective and sometimes better-tolerated protease inhibitor. However, between 1996 and 2006, most protease inhibitors tended to cause some degree of diarrhea or

frequent bowel movements, particularly treatments such as nelfinavir (Viracept) and lopinavir-ritonavir (Kaletra). Although these drugs were associated with weight gain, reports of obesity were not common in the late 1990s or early 2000s among HIV-positive people.

#### Nucleosides

A group of older anti-HIV drugs called nucleoside analogues (commonly called “nukes”) was widely used before and immediately after 1996. These older drugs included the following:

- d4T (stavudine, Zerit)
- AZT (zidovudine, Retrovir)

Both of these drugs are called thymidine analogues. The use of d4T and to a lesser extent AZT was associated with strange changes in body shape, including the accumulation of fat in the belly. As a result, leading guidelines do not recommend that they be used today. Instead, commonly used nukes nowadays are as follows:

- tenofovir DF + FTC (sold in a pill called Truvada and also available in generic formulations)
- abacavir + 3TC (sold in a pill called Kivexa and also combined with another drug and sold in a pill called Triumeq)

These nukes are generally well tolerated and do not cause changes in body shape, though tenofovir DF (TDF) is associated with an increased risk for kidney injury and bone loss. Abacavir is associated with an increased risk for heart attack among a minority of people in some studies. 3TC and FTC tend to be very well tolerated and are not by themselves associated with weight gain.

A newer formulation of tenofovir, called tenofovir alafenamide (TAF), is increasingly being used. This formulation of tenofovir is generally safer than the older one (TDF). A pill containing TAF + FTC is sold under the brand name Descovy. TAF is also co-formulated with other medicines in a single pill and sold under brand names such as Biktarvy, Genvoya and Odefsey. We will have more to say about TAF; in some studies it was associated with weight gain.

#### Non-nukes

Another group of drugs that were widely used starting in 2000 were non-nukes (NNRTIs), such

as efavirenz (Sustiva and in Atripla) and nevirapine (Viramune). These drugs did not generally cause diarrhea but, especially in the case of efavirenz, could have a range of side effects on the brain and mood. They were generally not associated with reports of obesity, though efavirenz sometimes could cause abnormal cholesterol levels. The commonly used non-nuke rilpivirine (Edurant and in Complera and Odefsey) is discussed later in this issue of *TreatmentUpdate*.

Finally, there is a new non-nuke called doravirine (Pifeltro and in Delstrigo). Detailed data about its impact on weight will be released over the coming months. Preliminary analysis suggests that it has a modest impact on weight.

Both non-nukes and protease inhibitors have additional drawbacks—they can interact with other drugs that HIV-positive people need, either raising or lowering the levels of these drugs in the body. Some drug interactions with these classes of medicines can be dangerous. Modern non-nukes, such as rilpivirine and doravirine, are generally well tolerated, though they all carry the potential of drug interactions.

### **Integrase inhibitors**

In 2007, the first integrase inhibitor, raltegravir (Isentress, twice daily) was introduced. In general, integrase inhibitors have few drug interactions and are well tolerated. Furthermore, integrase inhibitors are very powerful and when used as part of ART can usually quickly reduce the amount of HIV in the blood to very low levels commonly called “undetectable.” As a result, leading treatment guidelines in the U.S. and other high-income countries privilege the use of integrase inhibitors.

The leading integrase inhibitors are dolutegravir (in Dovato, Juluca, Tivicay and Triumeq) and bictegravir (in Biktarvy). A new formulation of raltegravir that can be taken once daily has recently become available.

An older integrase inhibitor, elvitegravir (co-formulated with other drugs and sold in pills called Genvoya and Stribild), is still used by some people. However, this drug must be taken with a small dose of the booster cobicistat. This latter drug is similar to a protease inhibitor and, like all protease inhibitors, cobicistat can cause gastrointestinal issues and interact with many other drugs.

### **ART, integrase inhibitors and weight gain**

Over the past several years, reports have emerged that some people who have used integrase inhibitors have gained weight. In most cases the increased weight is probably associated with a return to health. However, in a minority of cases, there have been substantial increases in weight. Many of the reports associated with weight gain and the use of ART are from study designs that could not yield definitive results—they were retrospective; they looked back on data previously collected for one reason and then re-analysed for another reason. Other studies were cross-sectional in nature—they only looked at data captured at one point in time. Both retrospective and cross-sectional studies are relatively cheap to conduct and can serve as a starting point for exploring an issue. However, interpreting the results from such studies can inadvertently increase the risk of drawing biased conclusions about the cause of an issue; in this case, weight gain. Trials of a more robust statistical design are expensive and time consuming. When randomized trials were done, weight was not always assessed or monitored as the main outcome of the study.

In this issue of *TreatmentUpdate*, we review studies that explore the issue of weight and body composition in HIV-positive people. When interpreting the data from such studies, bear in mind the following:

- Changes in the broader population – being overweight and obesity now appear to be more common among HIV-negative people than they were decades ago. This suggests that some of the factors that are driving weight gain in HIV-negative people are also possibly driving weight gain in HIV-positive people.
- HIV causes chronic and excess inflammation and activation of the immune system – taking ART and achieving and maintaining a suppressed viral load significantly reduces but does not normalize inflammation and immune activation. Among HIV-negative people, chronic inflammation contributes to an increased risk for many conditions, including obesity. It is plausible that the chronic inflammation seen in HIV infection also plays a role in increasing the risk for weight gain and obesity over the long term.

- Clinical trials of ART did not usually compare the physical activity and diet of participants. So the effect of these factors on weight gain/loss is not known.

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## B. Study finds fat goes up, muscle goes down over time

As all people age, they gradually lose muscle mass and probably gain some fat. Over decades, the loss of muscle mass can contribute to weakness and even frailty. Among HIV-negative people, this loss of muscle mass is initially small and tends to occur after the age of 50.

Studies of changes in body composition (usually such studies focus on the amount of fat and/or muscle in the body) in HIV-positive people have usually been short, rarely exceeding a monitoring period of 96 weeks. However, the restorative effects of HIV treatment (ART) on the immune system are so profound, that scientists increasingly expect many HIV-positive people to have near-normal life expectancy. Therefore, it is important that studies with HIV-positive people get the necessary funding so that they can continue for many years.

A team of scientists at the University of Modena in Italy has collaborated with other scientists in Canada, the U.S. and Portugal to analyse changes in body composition among ART users over the course of a decade. The scientists examined data from nearly 2,600 HIV-positive Italian people and found that muscle mass in the arms and legs “steadily declined.” Unlike what has been reported for HIV-negative people, the loss of muscle mass occurred even in HIV-positive people who were younger than 50 years old. Muscle loss occurred in both men and women.

The scientists also found that both men and women gained fat in their chest, abdomen and limbs during the same period.

The increase in fat in the body can contribute to a heightened risk for cardiovascular disease, diabetes and other problems.

The Italian study sounds an alarm that unfavourable trends are occurring among some HIV-positive people and interventions are needed so that the impressive gains in the survival brought about by ART are not lost to conditions affected by excess weight and fat.

### Study details

Scientists began collecting data from ART users in Modena in 2004. As part of the study, technicians

performed low-dose X-ray scans called DEXA (dual-energy X-ray absorptiometry) once or twice yearly for up to 10 years.

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

- age – 44 years (90% of participants were younger than 50 years old)
- 1,759 men and 839 women
- 76% had an undetectable viral load as a result of taking ART
- current CD4+ count – 530 cells/mm<sup>3</sup>
- ever had a CD4+ count less than 200 cell/mm<sup>3</sup> – 50% of participants
- history of AIDS-related weight loss – 5% men, 13% women
- duration of ART usage – 9 years
- all participants were white
- body mass index (BMI) – 23 kg/m<sup>2</sup>
- current smoker – 42%
- minimal exercise – 61%

The study collected data for up to 10 years, but most people were in the study for five years.

## Results

Here are the key findings:

### Muscle mass

Over the course of the study the amount of muscle tissue in participants consistently declined. This decline occurred in both men and women. Although the loss of muscle mass was more significant in people over the age of 50, it also occurred in people who were younger than 50 years old and, in some cases, people younger than 35 years of age. Loss of muscle tissue in relatively young HIV-negative people is unusual and the scientists found it striking that it occurred in young otherwise healthy HIV-positive people in their study.

On average men lost 322 grams and women 231 grams of muscle each year.

Factors associated with the loss of muscle mass included the following:

- among women – smoking and use of the older form of tenofovir (TDF, tenofovir disoproxil fumarate)

- among men – being older than 45 years, a history of AIDS-related weight loss and a CD4+ count that fell below the 200 cell/mm<sup>3</sup> mark at some point in the past

### Fat mass

Overall, scientists found that many participants gained fat over the course of the study. Furthermore, they noted: “These increases in fat mass were over and beyond those associated with ART initiation, and occurred in all age groups and across all ART classes and both sexes.”

The use of testosterone replacement therapy among some men did not appear to have an impact on the increase in fat mass.

The steady increase in fat mass is consistent with reports from other studies.

Factors associated with increased fat mass included the following:

- women – being female increased the chances of gaining fat mass
- men and women – use of TDF and integrase inhibitors, little or no exercise, and having a CD4+ count that fell below the 200 cell/mm<sup>3</sup> mark at some point in the past

### Bear in mind

1. The Italian study was observational in design. Such studies can find associations between the use of a certain drug or classes of drugs and, in this case, changes in body composition. However, due to built-in limitations, observational studies can never prove what scientists call “cause and effect.” In this case, an observational study cannot prove that exposure to TDF and/or integrase inhibitors caused an increase in fat mass.
2. The reasons underpinning the use of TDF and/or integrase inhibitors were not clear. As these reasons are unknown, the choice of which people used which regimen was not random. Thus, there could have been unmeasured factors that caused some people to use certain drugs or classes of drugs. These unmeasured factors could have introduced inadvertent bias when scientists drew their conclusions about TDF and integrase inhibitors. Therefore, we urge readers to treat the conclusions drawn about those drugs in

this study with much caution. Other reports in this issue of *TreatmentUpdate* will deal with the issue of anti-HIV drugs and weight gain.

3. Many medicines unrelated to HIV treatment can cause weight gain (usually fat). None of these were taken into account when analysing the data. This omission is another potential confounding issue. More about such medicines will be reported later in this issue of *TreatmentUpdate*.
4. The Italian study did have strengths—it monitored people over time and it included large numbers of women. Another strength is that it used objective measures of body composition: DEXA scans done at one clinical centre. Also, the Italian study monitored participants longer than is usually done in studies of body composition and HIV infection. Therefore, the overall findings from the Italian study—sustained decrease in muscle and increase in fat—are likely occurring to some degree in other populations of HIV-positive people.
5. The importance of the present study is that it sounds an alarm. Similar to HIV-negative people who are aging, a large (2,600-person) group of HIV-positive people is showing troubling trends of muscle loss and fat gain, but these seem to be occurring at a younger-than-expected age range. If these changes in body composition are sustained, there may be problems ahead.

### Addressing aging

If the full life-extending benefits of ART are to be realized, attention needs to be paid to what are commonly thought of as conditions of aging. This means that patients under the guidance of their healthcare providers have to engage in the hard work of maintaining a healthy life. This hard work will likely result in better quality of life as the onset of aging-related conditions (cardiovascular disease, pre-diabetes, diabetes, frailty, etc.) are delayed and their consequences minimized. Although some factors associated with trends in the present study were ones that participants likely had little control over, such as a history of low CD4+ cell counts, some issues they could control. For instance, about 40% of participants smoked and about 60% did not exercise regularly. These two issues can have a tremendous impact on overall health, mood, quality of life, and risk for stroke, heart attack and

cancer, and so on. The results of the present study are a call to action.

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## C. Changes in weight before and after ART became available

Scientists with large clinics in the United States and Canada conducted an analysis of changes in weight among 14,000 HIV-positive people who initiated HIV treatment (ART) between 1998 and 2010. They found that the proportion of people with obesity *prior* to ART initiation doubled from 9% in 1998 to 18% in 2010.

On average, three years after initiation of ART, 22% of people who entered the study with a normal weight had become overweight and 18% of people who were overweight at the start of the study had become obese.

### Study details

North America's premier HIV observational database, NA-ACCORD, has published many important analyses related to the health and wellbeing of HIV-positive people. One NA-ACCORD study that has often been overlooked focused on weight gain before and after the initiation of ART. In this study, clinics in Southern Alberta and Montreal contributed data.

### A note about BMI

Body mass index (BMI) is obtained by dividing a person's weight (in kilos) by their height (in metres) squared. BMI is a crude assessment of a person's relative fatness or thinness. A high BMI tends to occur in people who are overweight or obese. However, people who are very muscular can also have a high BMI and it can give a misleading impression of their fatness. What is considered a

normal BMI can vary from one continent and one ethno-racial group to another. Still, BMI is a cheap and simple way to find broad trends in data and is often used in studies.

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

- 83% men, 17% women
- age – 40 years
- major ethno-racial groups: white – 43%; black – 38%; Hispanic – 15%
- CD4+ count – 241 cells/mm<sup>3</sup>
- viral load – 50,000 copies/mL
- commonly used regimens were based on protease inhibitors or non-nukes

On average, participants were monitored for three years.

## Results

Scientists found that the proportion of people who were obese at the time they initiated ART increased significantly over the course of the study from 9% at the beginning to 18% by the end of the study.

## Weight gain

Scientists also found that people who were underweight or of normal weight at the time they entered the study were significantly more likely to gain weight than people who entered the study being overweight or obese. Other points related to weight gain included the following:

- Most (80%) of the increase in weight occurred during the first year of using ART.
- Regardless of their race/ethnicity, men experienced what the scientists called “a sharp early rise in weight while women showed a more uniform rise over three years.”
- In general, scientists found that people who had lower pre-ART CD4+ cell counts and higher viral loads were more likely to subsequently gain weight after ART initiation.

## Trends in time

According to the scientists, in the early years of the study (1998 to 2002) participants “tended to gain weight during the first year [which] then reached a plateau or fell in the subsequent two years.” In

the latter years of the study, scientists found that “weight gain continued over the full three years.”

## Trends in weight categories

After one year of using ART, scientists found that “20% of participants who had entered the study with a normal BMI had become overweight, and 15% of those overweight at baseline had become obese.”

They also found that three years after initiating ART, “22% of participants with a normal BMI at ART initiation had become overweight, and 18% of those overweight at baseline had become obese.”

The scientists noted that a shift after three years of ART “from normal BMI to overweight was most common among white males (23%), while a shift from overweight to obese was more common among [women of colour—21%].”

## Bear in mind

The NA-ACCORD analysis is derived from a large well-designed study. It has confirmed broad trends seen in other analyses and in society. Even before ART is initiated, the proportions of HIV-positive people who are overweight and obese have been on the rise in North America.

Other points:

- Women of colour seem to be particularly affected by increased weight after ART initiation; this has been seen in randomized clinical trials.
- The greater the degree of immune deficiency (indicated by low CD4+ cell counts combined with higher viral loads), the greater the subsequent increase in weight. This suggests that there may be something caused by HIV infection itself that contributes to subsequent weight gain after ART initiation.
- Integrase inhibitors were not widely used to initiate ART in the present study. The vast majority of people in the NA-ACCORD analysis used regimens anchored by protease inhibitors or non-nukes. This shows that older regimens are associated with weight gain.

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1. Koethe JR, Jenkins CA, Lau B, et al. Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. *AIDS Research and Human Retroviruses*. 2016 Jan;32(1):50-58.

## D. Dolutegravir and TAF or TDF—safety issues and weight gain

Scientists in South Africa and Cameroon conducted two randomized clinical trials of dolutegravir-based regimens. These trials have yielded important safety information as well as data about weight gain. The findings from these studies confirm general trends that we will report on later in this issue of *TreatmentUpdate*.

### The ADVANCE study in South Africa

In South Africa, scientists conducted a randomized 96-week study of the following once-daily regimens used to initiate HIV treatment (ART):

- dolutegravir + TDF (tenofovir disoproxil fumarate) + FTC
- dolutegravir + TAF (tenofovir alafenamide) + FTC
- efavirenz + TDF + FTC

Study coordinators enrolled 1,053 HIV-positive people who initiated ART with one of the above regimens. Notably, nearly 60% of participants in ADVANCE were women and 99% were black.

### Results

Not surprisingly, all three regimens worked well. We won't explore the effects of the medicines on viral load and CD4+ cell count, as such effects have been well established in clinical trials beginning nearly a decade ago for dolutegravir and even longer for efavirenz. Instead, we focus on some safety issues and weight.

### Sleep

Overall, dolutegravir-containing regimens were well tolerated. There were generally no significant differences in sleep quality and the time spent sleeping among the different regimens. However, the scientists stated that “there were slightly more reported cases of [severe or very severe] insomnia

in the TAF-based group than in the other groups but no discontinuation of the trial regimen due to insomnia.”

### Fetal safety

As detailed in *TreatmentUpdate* issue 233, there have been reports of five babies born to HIV-positive mothers in the southern African country of Botswana who were born with a type of birth defect called neural tube defects. All mothers were taking dolutegravir at the time of conception.

In the ADVANCE study, a total of 78 women became pregnant; 50 of them were taking dolutegravir during pregnancy. None of their babies were born with neural tube defects. Ten percent of the pregnancies are ongoing.

### Focus on weight

According to the scientists, “absolute weight gain and the percentage of patients in whom obesity emerged during treatment were highest in the TAF-based group (6 kg, 14% new obesity), but the values in the TDF-based group (3 kg, 7% new obesity) were also higher than those in the standard-care group [efavirenz: 1 kg, 6% new obesity].”

Furthermore, scientists added that “weight gain was significantly higher in female than in male patients across all three groups with no clear plateau in the increase.”

Obesity tended to occur by week 48 and was associated with the following factors upon study entry:

- lower CD4+ cell count
- higher viral load
- older age

### ANRS 12313 (NAMSAL)

In Cameroon, another randomized clinical trial called NAMSAL enrolled 613 HIV-positive people, a majority of whom (66%) were women. All participants were initiating ART that consisted of one of the following regimens:

- dolutegravir + TDF + 3TC
- low-dose efavirenz (400 mg) + TDF + 3TC

All medicines were taken once daily and data were reported after 48 weeks.

### Results—Focus on weight gain

On average weight gain was observed in more participants who took dolutegravir than low-dose efavirenz, as follows:

- dolutegravir – 5 kg; 12% new obesity
- efavirenz – 3 kg; 5% new obesity

A total of 25 women became pregnant during the study, 13 who were taking dolutegravir and 12 who were taking efavirenz. No birth defects were found in their infants.

### Putting it all together

The data from ADVANCE and NAMSAL show that commonly used regimens in parts of sub-Saharan Africa these days are associated with weight gain, in particular, the combination of dolutegravir and TAF. However, other factors also associated with weight gain were as follows:

- lower CD4+ cell count
- higher viral load
- older age

The fact that having a lower CD4+ cell count and a higher viral load were both associated with weight gain suggests that HIV does something to the immune system that increases the risk of weight gain. This finding is yet another reason to initiate ART early in the course of HIV infection.

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### E. An analysis of randomized clinical trials and weight gain

In studies reviewed earlier in this issue of *TreatmentUpdate*, we examine data captured from as early as a few years after the introduction of potent HIV treatment (ART) to about 2010. In that era, commonly used drugs used to anchor a regimen were non-nukes (such as efavirenz and nevirapine) and protease inhibitors (such as ritonavir, indinavir, saquinavir, nelfinavir, lopinavir and atazanavir). However, analyses from that era have shown that obesity was occurring among some HIV-positive people even *before* they initiated ART. Furthermore, obesity increased after initiation of ART. Note that issues such as being overweight and obesity are also increasing in the population of HIV-negative people.

In the current era, many people who initiate ART in Canada and other high-income countries are most likely to have a regimen anchored by an integrase inhibitor. Today, that is most commonly bicitegravir (in Biktarvy) or dolutegravir (Tivicay and in Dovato, Juluca and Triumeq). A new once-daily formulation of the integrase inhibitor raltegravir (Isentress HD) is available in high-income countries. However, it is not commonly used because it is not co-formulated with other drugs.

In a paper in press in the journal *Clinical Infectious Diseases*, a team of scientists with the pharmaceutical company Gilead Sciences along with some physicians in Europe and the United States reviewed data from randomized clinical trials in which ART was initiated in more than 5,000 people between 2003 and 2015. They found that, overall, weight gain occurred in all clinical trials and with nearly all drugs used. However, the team stated that “weight gain was greater in more recent [clinical] trials and with use of newer ART regimens.”

Factors prior to ART initiation that played a role in subsequent weight gain were as follows:

- lower CD4+ cell counts
- higher viral loads
- not injecting street drugs
- being female
- being black

We now report on comparisons among different regimens and classes of anti-HIV drugs done by the team.

## Study details

The study team focused on regimens that were in the final stage of clinical trials (phase III) prior to licensure. All participants were monitored for about two years.

At the start of the studies, the distribution by weight of participants was as follows:

- normal weight – 52%
- overweight – 31%
- obese – 16%

(Numbers do not total 100 due to rounding.)

## Results

Overall trends were as follows:

- People who entered the more recent trials tended to be heavier and have higher CD4+ cell counts prior to initiating ART.
- Weight gain occurred regardless of the regimen used.
- Weight gain was greater in more recent clinical trials (these tended to have newer drugs).
- Newer regimens were associated with greater weight gain than older regimens.
- On average, people gained about 2 kg of weight.
- The greatest weight gain tended to occur within the first year of the study.

## Risk factors for weight gain

### CD4+ cell count

As with other large analyses, participants who entered the Gilead studies with less than 200 CD4+ cells/mm<sup>3</sup> gained more weight (nearly 3 kg) than participants who entered the study with a CD4+ count greater than 200 cells/mm<sup>3</sup>.

### Viral load

People who entered a study with a viral load greater than 100,000 copies/mL gained about 1 kg more than people who had a lower viral load at study entry.

## Symptoms and AIDS

People who had symptoms of AIDS or symptoms of immune deficiency gained half a kilogram more than symptom-free people.

## Not injecting street drugs

People who did not inject street drugs gained 1.4 kg more than people who injected street drugs.

## Race/ethnicity

Black people generally gained about 1 kg more in weight compared to non-Black people.

## Gender

Women gained more weight than men. The greatest weight gain occurred among women who were black. The second-greatest weight gain was seen among men who were black.

## Types of ART

All major classes of ART were associated with weight gain, as follows:

- integrase inhibitors – 3.24 kg
- non-nukes – 1.93 kg
- protease inhibitors – 1.72 kg

These differences in weight gain were statistically significant when comparing weight gain with integrase inhibitors to other classes of ART.

## Integrase inhibitors

Weight gain was greatest among integrase inhibitors:

- bictegravir – 4.2 kg
- dolutegravir – 4.07 kg
- elvitegravir – 2.72 kg

## Non-nukes (NNRTI)

Among non-nukes, participants who took rilpivirine (in Complera and Odefsey) gained more weight than people who took efavirenz:

- rilpivirine – 3.01 kg
- efavirenz – 1.7 kg

## Nucleoside analogues (nukes)

Compared to the oldest nuke (AZT, zidovudine, Retrovir and in Combivir and Trizivir), participants who took other nukes more commonly used today gained substantially more weight as follows:

- tenofovir alafenamide (TAF, the newer and safer form of tenofovir) + FTC – 4.25 kg

- abacavir (often this is co-formulated with 3TC) – 3.08 kg
- tenofovir disoproxil fumarate (TDF, the older formulation of tenofovir) + FTC – 2.08 kg

People who took AZT generally gained about 0.39 kg.

### Risk factors for gaining 10% or more of baseline body weight

The team focused on the 10% figure because this is usually clinically significant; they called such weight gain “extreme.” Such an increase occurred in nearly 13% of participants.

Factors at the start of the study that were associated with an increase of 10% or more of body weight were as follows:

- lower CD4+ cell count
- higher viral load
- having a normal body mass index (BMI) vs. being overweight or obese
- being female
- being black

### Comparing different drugs and an increase in body weight of 10% or more

The team used the non-nuke efavirenz (in Atripla and Sustiva, Stocrin) as a reference when comparing the impact of other drugs on weight gain of 10% or more and found that initiating a regimen containing any of the following drugs was associated with an increased risk for a large degree of weight gain:

- bictegravir
- dolutegravir
- elvitegravir
- rilpivirine

However, the use of atazanavir with a small dose of ritonavir (this is called “boosted atazanavir”) in a regimen was not associated with a large increase in weight.

Among nukes, the scientists found that initiating a regimen containing TAF (this is usually co-formulated with FTC) was associated with a significantly increased risk of gaining 10% or more

of body weight. In contrast, the following nukes were not associated with such a risk for weight gain:

- TDF (this is usually co-formulated with FTC)
- abacavir (this is usually co-formulated with 3TC)

### Metabolic issues—Good and bad news

In general, the team did not find clinically significant increases in measures of fasting blood sugar or blood pressure during the study. Increased weight was not associated with an increased risk for type 2 diabetes. However, participants in phase III clinical trials (of HIV treatment or non-HIV treatment) tend to be relatively healthier than the average person with the same condition in the community. Also, participants were monitored for about two years. This is both good and bad news. The good news is that the findings likely mean that in the short-term (two years) the increase in weight does not generally cause metabolic problems. However, the bad news is that studies among HIV-negative people have generally found that weight gain over the long-term is associated with a range of health problems.

### Note well

The present studies were not designed primarily to assess weight gain. The studies were meant to assess the effectiveness and general safety of ART. Yet, their findings about weight gain concur with what leading physicians are seeing in their clinics with some patients and with reports from other randomized and observational studies. Additional clinical trials with a focus on weight, metabolic and cardiovascular issues are now needed to monitor ART users over the long term and to help find ways to safely lose weight if necessary. Although all modern HIV regimens are generally associated with some degree of weight gain, the good news is that most people who use ART do not become obese. In the short-term (two years), the increased weight was usually a few kilograms.

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## F. Why are some people with HIV becoming heavier?

As reported earlier in this issue of *TreatmentUpdate*, initiating HIV treatment (ART) is generally associated with an increase in weight. We now explore possible reasons for this.

Some of the risk factors for weight gain prior to initiating ART that were reported earlier in this issue were immunological (having a low CD4+ count) or virological (having a high viral load). These findings, also reported in earlier studies, point to an additional benefit for starting HIV treatment long before immune deficiency has developed.

### History

Looking back on the history of HIV treatment, most of the early pivotal clinical trials of ART have occurred in white men in high-income countries. Such studies did not generally have sufficient numbers of women and people of colour to make meaningful statistical comparisons of weight differences between genders or ethno-racial groups. Furthermore, most, if not all, of these studies were not primarily designed to assess changes in weight and body mass index (BMI) among regimens. In recent years, phase III clinical trials have included more women and people of colour.

### The good news

It is important to note that most people who took ART in pivotal clinical trials did not become obese. However, the findings from recent studies of ART initiation that analysed weight suggest that both healthcare providers and patients need to become more vigilant about monitoring weight and need to intervene quickly when excess weight gain occurs.

## Choosing regimens

In general, newer HIV treatment regimens are better tolerated and more effective than older regimens. Newer treatments, particularly integrase inhibitors, tend to have the fewest potential drug interactions. It is very unlikely that doctors and patients will return to using older regimens due to the issue of weight gain.

Not only are older drugs less powerful, they have distinct disadvantages. Long-term use of AZT has been associated with an increased risk for loss of muscle mass and abnormal changes in body shape (the lipodystrophy syndrome). Efavirenz is associated with an increased risk for neuropsychiatric effects, including dizziness, depression and subtle paranoia in both the short- and long-term. This drug also is associated with an increased risk of thoughts of suicide and attempts at suicide. Despite these issues, some people who initiated efavirenz-based treatment years ago seem to tolerate it well.

Rather than avoid initiating treatment with integrase inhibitors (such as bictegravir, dolutegravir, elvitegravir and raltegravir) and nucleotide analogues such as TAF solely because of concerns about potential weight gain, it may be useful for healthcare providers and patients to check trends in weight prior to and after starting or switching regimens. It may also be useful for healthcare professionals to discuss with patients issues that have the potential to impact weight gain, such as the following:

### Physical activity

Are people with HIV getting enough daily physical activity, including walking and climbing stairs? Can they begin a program of exercise? See this article in *TreatmentUpdate 234* about different forms of physical activity: Exercise as medicine

### Sleeping problems

Rest and sleep quality are sometimes overlooked aspects of health. A large observational study in HIV-negative people found that people who have sleeping problems tend to gain weight. Assessing sleep problems in patients who are unexpectedly gaining weight may be useful.

### Emotional and mental health

Are there factors in a person's life that can affect how they respond to stressful events? For instance, when stressed, some people eat more fat and

carbohydrate-rich foods as a source of comfort. Repeated engagement in excessive intake of carbohydrates and fatty food can lead to weight gain over time. Depression can affect appetite—some people gain weight, others lose weight. Is a person who is gaining weight experiencing depression and/or anxiety?

### **Metabolic conditions, hormones and arthritis**

Some conditions and life-stages are associated with weight gain, including the following:

- diabetes
- problems with the thyroid gland and its hormones
- women who are post-menopausal
- arthritis

### **Diet**

Not everyone follows a diet that is informed by dietary guidelines. If subsidized access to dietary counselling is available (sometimes this is provided in large hospitals and clinics), consultation with a registered dietician may prove fruitful. Registered dietitians can assess the quality and quantity of meals, and if necessary, provide helpful advice about making healthy changes.

### **Substance use**

Alcohol contains calories. Is excess consumption of alcohol an issue? Excess consumption of alcoholic beverages could suggest unaddressed mental health and emotional issues.

Healthcare professionals, including pharmacists, can review the non-HIV medicines a patient is taking to assess their potential impact on weight.

### **Focus on HIV treatment in weight gain**

How might ART play a role in excess weight gain in some people? At this time there are no definitive answers, though some scientists have theories that relate to the following issues/drugs:

#### **Integrase inhibitors**

One theory is that dolutegravir (and possibly bictegravir and other integrase inhibitors) interacts with a receptor called MC4R (melanocortin 4 receptor). This receptor is found on cells in the brain and plays a role in maintaining energy balance. MC4R can affect appetite and weight. It is possible that integrase inhibitors interact with MC4R in a way that leads to increased appetite and

weight gain. However, research with HIV-positive people and MC4R has not been undertaken. It is likely that scientists would first conduct experiments with cells, HIV, integrase inhibitors and this hormone. If there is a signal that MC4R is affected by integrase inhibitors, then perhaps the next step might be experiments with monkeys infected with SIV (simian immunodeficiency virus). This virus causes an AIDS-like condition in susceptible monkeys and is closely related to HIV.

#### **Setmelanotide**

Studies with HIV-negative people have found that some experimental drugs that interfere with MC4R can result in reduced appetite and cause people to lose weight.

One candidate drug that interferes with MC4R is called setmelanotide. It has completed pivotal clinical trials in people with obesity linked to certain genes. In these trials, significant reductions in appetite and weight occurred. Preliminary results suggest that the drug is generally safe, though darkening of the skin and hair can occur. The FDA is currently reviewing an application for approval of setmelanotide by Rhythm Pharmaceuticals and hopefully will approve the drug in 2020. However, setmelanotide needs to be tested in general cases of excess weight and obesity. It has been granted orphan drug status by the FDA. The designation of orphan drug is given to medicines that are used for a relatively small market. Drugs that have this designation are usually very expensive, though at this time a price for setmelanotide has not been made publicly available.

Against the theory that integrase inhibitors interfering with MC4R is the sole cause of weight gain in HIV-positive people who use this class of drug are these observations:

- As mentioned earlier in this this issue of *TreatmentUpdate*, studies have found that some HIV-positive people appeared to be gaining weight even before they began to use ART.
- Increases in weight have been reported with different classes of ART, though the latest anti-HIV drugs, such as dolutegravir, bictegravir and TAF seem to have the greatest association.

#### **Gut bugs**

Scientists use the term *microbiome* to describe the collection of bacteria, fungi and viruses that live in the body. The intestines of HIV-positive people

have been found to contain imbalances in the population of bacteria and fungi that naturally live there. Initiating ART and continuing to take it can only partially correct this imbalance, and clinical trials with supplements of friendly gut bacteria are underway. Such clinical trials could assess possible changes in weight as an outcome.

### Inflammation

HIV infection is associated with excessive levels of inflammation and activation of the immune system. Initiating ART and achieving and maintaining an undetectable viral load helps to significantly reduce but not eliminate the excess inflammation and immune activation associated with HIV. Studies in HIV-negative people suggest that chronic inflammation can contribute to gaining excess weight. It is therefore possible that HIV-associated chronic inflammation and immune activation may contribute to excess weight in some people.

### Other reasons

There may be other, as yet unknown reasons, that ART is associated with substantial weight gain in some people. One important point to bear in mind is that, in general, HIV-negative people are becoming heavier and the reasons for this are not clear. The factors driving weight gain in HIV-negative people are likely also affecting HIV-positive people. Some scientists think that these days people are generally eating more food, possibly more highly processed food, and, perhaps in some cases, getting less physical activity than they did decades ago. The study in Italy reported earlier in this issue of *TreatmentUpdate* found that nearly 50% of about 2,600 HIV-positive people were getting no or minimal levels of daily exercise. This shows that among some people a lack of physical activity is a major issue. Other scientists suspect that contaminants in the environment may contribute to the risk of gaining weight. Whatever the cause, much research on weight gain in general and in some ART users lies ahead. Such research will take time.

### For the future

Medical doctor Sara Bares at the Nebraska Medical Center has reviewed the analysis of randomized clinical trials by Gilead Sciences. She raised the

following questions that need to be answered in future research:

- “What do we do for patients who experience severe weight gain following ART initiation?”
- “How long does this weight gain persist?”
- “Will a switch to an alternative regimen reverse or attenuate some of this weight gain? If so, what regimen should they choose?”
- “Is an adjustment in both the backbone and anchor agent needed?” The term *anchor* agent refers to the most potent drug in a regimen. The nucleoside analogues (nukes) that usually accompany a regimen are referred to as the *backbone* by doctors and scientists.
- “Will adjustment in the route of administration alter the side effect profile (i.e. will long-acting injectable therapy be associated with similar amounts of weight gain)?”

These questions can help guide some future research on weight gain in HIV-positive people.

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## G. Non-HIV drugs associated with weight gain

As scientists move forward with studies of HIV-positive people and weight gain, it is important to take into account the presence of non-HIV drugs that have the potential to cause weight gain. In many of the studies that have reported weight gain in HIV-positive people in the current era, there was a lack of information about other medicines that some participants may be taking that could also have caused weight gain.

Doctors in Belgium who study diabetes have scoured the scientific literature and assessed the potential of some medicines (and health conditions) to cause weight gain among HIV-negative people. The findings in this population likely also apply to HIV-positive people. It is best

to discuss all medicines being taken with a doctor and pharmacist who can reveal which categories of medicine a person is taking and the *potential* of the medicine to cause weight gain.

### Note well

Below is a summary of the doctors' findings, where the drugs listed have been associated with weight gain. This does not mean that a particular drug on the list will cause weight gain in everyone who uses it. However, it does mean that the *risk* of weight gain when using the mentioned drug is generally increased. In some people, the weight gain may occur over a long period and may only consist of a few kilos.

In many of the studies reviewed by the Belgian doctors that found an association between weight gain and a drug or class of drugs, it is not clear if the amount of daily physical activity exerted by participants was taken into account. Therefore, the list below is something that should not be read as definitive. Rather, it should be seen as something that can be considered for discussion between doctors and their patients.

As mentioned earlier in this issue of *TreatmentUpdate*, there are at least several issues associated with weight gain that have nothing to do with medicines and those also need to be considered whenever weight gain occurs.

### Antidiabetic agents

Insulin, sulfonylurea and glitazones

### Drugs to treat higher-than-normal blood pressure

Some beta-blockers (results can vary from one person to another; that is, some people can gain weight while others do not when they initiate treatment with beta-blockers)

### About mental health issues and weight

Drugs that are used to treat mental health conditions are called psychotropic medicines. In general, obesity is more common among some people with mental health conditions than among people without such diagnoses. According to the Belgian doctors, the following factors likely play a role in the weight gain seen in people with mental health conditions: "an unhealthy diet, insufficient physical activity, and a high prevalence

of smoking or other substance [use] accompany many psychiatric illnesses.”

The doctors also note that many mental health conditions affect a part of the brain called the hypothalamus as well as the pituitary and adrenal glands (the HPA axis). These three parts of the body produce hormones that can affect hunger, appetite and weight. Mental health conditions can overstimulate these parts of the body, leading to chronic elevated levels of the hormone cortisol. In turn, elevated levels of this hormone can give rise to the buildup of fat deep in the belly (visceral fat). This type of fat produces hormones that can cause inflammation and feed the buildup of further visceral fat, causing a vicious cycle. Doctors have found that in some cases obesity can contribute to depression and depression can contribute to obesity.

It is important to note that it is sometimes difficult for doctors to assess the precise effect of psychotropic medicines on weight gain, as stated by the Belgian doctors, “because the underlying psychiatric disorder itself can be characterized by changes in appetite and physical activity.” The doctors further stated that “weight gain in the first month after the start of treatment is a strong predictor of long-term weight gain. Therefore, weight should be monitored before and shortly after starting psychotropic drugs and a 5% increase above baseline weight after the first month should prompt physicians to reconsider therapeutic options or to initiate weight-controlling strategies.”

The doctors noted that mental health conditions and related treatments seem to cause more weight gain in women than men.

### **Antidepressants**

Although antidepressants are prescribed for the treatment of depression, they are sometimes used by doctors for the treatment of anxiety or depression that is associated with symptoms of anxiety.

Tricyclic antidepressants are older antidepressants that are seldom used as first- or second-line treatment for anxiety or depression today. However, tricyclic drugs generally cause some degree of weight gain.

Other classes of drugs that affect mainly serotonin and/or norepinephrine—so-called SSRIs (including citalopram, fluoxetine and sertraline) and SNRIs

(including venlafaxine and duloxetine)—can cause temporary weight loss or have a neutral effect on weight.

Paroxetine seems to be the SSRI with the greatest potential for weight gain.

Bupropion can reduce appetite and thus weight. In clinical trials, a combination of naltrexone and bupropion has been found to reduce weight in people with obesity.

An older antidepressant mirtazapine is associated with weight gain.

The newer and widely used antidepressant vortioxetine (Trintrellix) was not analysed by the Belgian doctors. However, analyses of clinical trials of this drug by other doctors suggest that it has a minimal effect on weight.

Lithium is associated with weight gain in some people.

### **Antipsychotics**

In addition to treating psychosis, second-generation antipsychotics are sometimes prescribed for the management of non-psychotic disorders such as the following: bipolar disorder, attention deficit hyperactivity disorder and dementia in elderly people. Examples of these drugs include the following: clozapine, olanzapine, quetiapine and risperidone. According to the Belgian doctors, all four of these medicines have the greatest potential for weight gain.

The doctors also noted that other second-generation antipsychotics, such as aripiprazole, amisulpride and ziprasidone, “are weight neutral or induce only minor weight gain.” They stated that newer drugs such as asenapine, iloperidone, lurasidone and paliperidone “also seem to have less metabolic side effects” compared to older drugs.

### **Antiseizure drugs**

This category of medicine is used to treat seizures, but some antiseizure drugs have also been used to treat nerve pain.

Some antiseizure drugs can cause weight gain, including the following: valproate and carbamazepine. Other antiseizure drugs, such as pregabalin and gabapentin, sometimes used to

treat pain arising from nerve injury can also cause weight gain.

Other antiseizure drugs, such as lamotrigine, levetiracetam and phenytoin, tend to have a neutral effect on weight.

Some anti-seizure drugs, such as felbamate, topiramate and zonisamide, can cause weight loss.

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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.**

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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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