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## I ANTI-HIV AGENTS

### A. Biktarvy becomes a treatment option in Canada

In July 2018 Health Canada licensed the sale and use of Biktarvy for the treatment of HIV infection. Biktarvy, manufactured by Gilead Sciences, is supplied as tablets and contains the following drugs:

- bictegravir – 50 mg
- TAF (tenofovir alafenamide) – 25 mg
- FTC (emtricitabine) – 200 mg

Of these three drugs, bictegravir is new. It belongs to a class of anti-HIV drugs called integrase inhibitors. Leading treatment guidelines in high-income countries recommend initiating combination treatment with an integrase inhibitor, as these drugs are generally well tolerated and highly effective. Integrase inhibitor combinations are also recommended for second-line use.

Each tablet of Biktarvy is a complete treatment and is taken once daily. Biktarvy can be taken with or without food, day or night.

Biktarvy has been tested as part of the initial treatment of HIV infection in clinical trials where it showed about the same level of general safety and effectiveness as the competing integrase inhibitor, dolutegravir (Tivicay and in Triumeq).

In this issue of *TreatmentUpdate*, we review recent clinical trials of Biktarvy in treatment-experienced people.

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Bear in mind that bicitegravir (the integrase inhibitor in Biktarvy) is new and has been tested in several thousand people in clinical trials. Many of these people were relatively young and healthy and side effects were generally mild. Once Biktarvy becomes subsidized by private and public drug plans, it will become more widely used in people who do not generally enter clinical trials. Such people may be older and/or have other conditions (co-morbidities) and in some cases may be ill. Their experience of side effects may be different than reported in pivotal clinical trials of Biktarvy. Also, as with any newly licensed medicine, the full range of side effects associated with Biktarvy, particularly rare ones, may not be known for at least another five years. However, the data collected so far suggests that Biktarvy is generally safe.

### Access

It will likely be weeks or months before Biktarvy appears on the lists of medicines covered by private insurance formularies. Gilead Sciences will shortly begin the process of negotiating the price of Biktarvy with provincial and territorial formularies. As this is a long process, Biktarvy is not likely to be subsidized by formularies until the Spring of 2019.

### REFERENCE:

Gilead Sciences Canada. Biktarvy. *Product Monograph*. 10 July, 2018.

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## B. Switching to Biktarvy from a protease inhibitor-based regimen

When used as part of combination HIV therapy (ART), the class of drugs called integrase inhibitors has potent anti-HIV activity and is generally well tolerated. As a result, more doctors are prescribing integrase inhibitors and more patients are using them.

Bicitegravir is a new integrase inhibitor and is supplied as part of an entire regimen in one pill called Biktarvy. Other medicines in Biktarvy are TAF (tenofovir alafenamide) and FTC (emtricitabine). This pill is taken once daily with or without food, day or night.

In one study, researchers in Canada and other countries recruited adults who were taking

regimens based on protease inhibitors and whose viral loads were undetectable. Participants were randomly assigned to receive either Biktarvy (290 people) or to continue with their protease inhibitor-based regimen (287 people). At the 48th week of the study, nearly all participants continued to maintain an undetectable viral load. In general, rates of side effects were similar regardless of the regimen used, although headache was more common in Biktarvy users.

### Study details

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

- 83% men, 17% women
- age – 48 years
- major ethno-racial groups: white – 66%; black – 27%; Asian – 2%; Indigenous – 1%
- CD4+ count – 620 cells/mm<sup>3</sup>
- 83% were free from symptoms related to HIV disease
- hepatitis B virus (HBV) co-infection – 3%
- hepatitis C virus (HCV) co-infection – 2%
- eGFR (estimated glomerular filtration rate; a general measure of kidney health) – 105 mL/minute

Commonly used protease inhibitors included the following:

- atazanavir (Reyataz)
- darunavir (Prezista)

Each of these drugs was taken with a small dose of another anti-HIV drug called ritonavir. The purpose of ritonavir is to raise and maintain the concentration of the protease inhibitor in the blood so that once-daily dosing of atazanavir or darunavir is effective.

In addition to protease inhibitors, study participants also took the following combinations of anti-HIV drugs:

- TDF (tenofovir disoproxil fumarate) + FTC (emtricitabine)
- abacavir + 3TC

The study took place for 48 weeks.

## Results

At the 48th week of the study, the proportions of participants with an undetectable viral load (less than 50 copies/mL) were distributed as follows:

- Biktarvy – 92%
- protease inhibitor regimen – 89%

Also, at week 48, the proportions of participants with a viral load less than 20 copies/mL were distributed as follows:

- Biktarvy – 86%
- protease inhibitor regimen – 85%

These differences were not statistically significant. Analysis suggests that, overall, Biktarvy is similar in effectiveness as the leading protease inhibitor-based regimens.

## Adverse events

In clinical trials, the term *adverse events* is used to describe the unfortunate occurrences that can happen. Some of these may be due to the underlying disease process, some to the study medicines and some have nothing to do with the study at all.

The proportions of participants with treatment-related adverse events were distributed as follows:

- Biktarvy – 19%
- protease inhibitor regimen – 2%

This difference between the two regimens was driven mostly by headache, distributed as follows:

- Biktarvy – 12%
- protease inhibitor regimen – 4%

Here is the distribution of some other side effects:

### Diarrhea

- Biktarvy – 2%
- protease inhibitor regimen – 0%

### Flatulence

- Biktarvy – 2%
- protease inhibitor regimen – 0%

### Nausea

- Biktarvy – 2%
- protease inhibitor regimen – 0%

In general, most side effects were of mild to moderate intensity and resolved over time.

## Focus on headache

According to the researchers, headache occurred within the first eight weeks of initiating therapy with Biktarvy. Headache was generally mild and gradually resolved in most participants.

By the 48th week of the study, participants who still reported headache were distributed as follows:

- Biktarvy – 2%
- protease inhibitor regimen – 1%

No one prematurely left the study because of headache.

## Serious adverse events

The distribution of serious adverse events was as follows:

Biktarvy – two people taking this regimen had to prematurely leave the study because of the following issues:

- rash – one person
- schizophrenia – one person; investigation suggested that schizophrenia was related to exposure to Biktarvy

Protease inhibitor regimen – one person taking this regimen had to prematurely leave the study because of the following reasons:

- bone fracture and kidney injury

## Deaths

Two deaths occurred during the study. One person taking Biktarvy was diagnosed with tumours in one lung that spread to the brain. One person taking a protease inhibitor regimen died from complications associated with head injury arising from violence. These deaths were unrelated to the study medicines.

## Abnormal lab test results

Serious or very seriously abnormal blood test results were distributed as follows:

- Biktarvy – 16%
- protease inhibitor regimen – 29%

This difference occurred mainly because of elevated levels of the waste product bilirubin among protease inhibitor users. Such elevations can occur in atazanavir users.

eGFR levels decreased very modestly in people taking Biktarvy and remained stable in people taking protease inhibitors. More sophisticated assessments did not find any treatment-related kidney injury.

Participants who received Biktarvy had statistically significant decreases in the following assessments done on fasting blood samples:

- total cholesterol
- LDL-C (“bad” cholesterol)
- triglycerides
- ratio of total cholesterol to HDL-C (“good” cholesterol)

Such changes are not surprising because participants who received Biktarvy had previously been taking protease inhibitors, which can cause unfavourable changes to fatty substances in the blood. In contrast, as a class, integrase inhibitors are known to have neutral effects on lipids in the blood.

## Bear in mind

The present study found that Biktarvy is an option for doctors and patients who want to consider moving away from HIV treatment based on protease inhibitors. Biktarvy is effective and generally safe. However, Biktarvy users can develop a mostly mild headache that gradually resolves.

## REFERENCE:

Daar ES, DeJesus E, Ruane P, et al. Efficacy and safety of switching to fixed-dose bicitgravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48-week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV*. 2018; *in press*.

## C. Switching from Triumeq to Biktarvy

Triumeq is the brand name of a pill containing the following three anti-HIV medicines:

- dolutegravir
- abacavir
- 3TC

Triumeq is a complete HIV treatment—taken once daily, with or without food, day or night—and is widely used. Clinical trials have found it to be highly effective and generally well tolerated, though some users have reported difficulty falling asleep and/or staying asleep.

Biktarvy is the brand name of a pill with the following three anti-HIV medicines:

- bicitgravir
- TAF (tenofovir alafenamide)
- FTC (emtricitabine)

Dolutegravir and bicitgravir belong to a class of drugs called integrase inhibitors.

In a double-blind study conducted in Canada and other countries, researchers recruited participants who were taking Triumeq and who had undetectable viral loads (less than 50 copies/mL) and randomly assigned them to receive one of the following:

- Biktarvy – 282 people
- continue taking Triumeq – 281 people

At 48 weeks, similar proportions of participants maintained an undetectable viral load. Although rates of side effects were greater among people who continued taking Triumeq, more people quit Biktarvy than Triumeq because of bothersome side effects.

## Study details

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

- 87% men, 13% women
- age – 46 years
- major ethno-racial groups: white – 73%; black – 21%; Asian – 3%; Indigenous – 2%
- CD4+ count – 700 cells/mm<sup>3</sup>

- 87% did not have symptoms of HIV disease
- hepatitis B virus (HBV) co-infection – no people
- hepatitis C virus (HCV) co-infection – 1 person
- eGFR (estimated glomerular filtration rate; a general measure of kidney health) – 101 mL/minute

## Results

At the 48th week of the study, the proportions of participants with a viral load less than 50 copies/mL were similar and distributed as follows:

- Biktarvy – 94%
- continued Triumeq – 95%

Also, at week 48, the proportions of participants with a viral load less than 20 copies/mL were distributed as follows:

- Biktarvy – 90%
- continued Triumeq – 91%

These differences were not statistically significant and suggest that both regimens have similar effectiveness. The technical term for this is that Biktarvy is “non-inferior” to Triumeq.

## Safety

The researchers stated that both regimens were “well tolerated” and most side effects that occurred were “mild or moderate in severity.”

Premature withdrawal from the study due to drug-related side effects was uncommon and distributed as follows:

- Biktarvy – 2% (six people)
- continued Triumeq – 1% (two people)

These side effects were distributed as follows:

### Biktarvy

- headache – two people
- abnormal dreams – one person
- stroke – one person
- vomiting – one person
- thoughts of suicide – one person

Investigation suggested that these issues were likely related to Biktarvy—all except for the thoughts of suicide, as researchers stated that the person had an “extensive psychiatric history” prior to entering the study.

### Triumeq

- headache – one person
- itchy skin – one person

Investigation suggested that both of these problems were likely related to the use of Triumeq.

The distribution of side effects that were not serious was as follows:

### Headache

- Biktarvy – 2%
- Triumeq – 3%

### Diarrhea

- Biktarvy – 1%
- Triumeq – 1%

### Abnormal dreams

- Biktarvy – less than 1%
- Triumeq – 2%

### Nausea

- Biktarvy – 0%
- Triumeq – 2%

### Difficulty falling asleep and/or staying asleep

- Biktarvy – 0%
- Triumeq – 1%

## Other issues

Between 2% and 3% of participants on each study regimen developed fractures. However, investigation revealed that these were not due to the study medicines.

Overall, when it came to measures of kidney health, there were no clinically significant differences between regimens.

## Deaths

Two people taking Biktarvy died. One person died because their heart stopped beating—a consequence of serious cardiovascular disease. Another person

died because of toxicity arising from excess intake of alcohol combined with opioids.

No one taking Triumeq died.

### Abnormal lab test results

About 3% of participants on each study regimen developed abnormal lab test results. No one suffered serious injury associated with these lab test results.

Overall, there were no clinically significant changes in routine laboratory measures of kidney and heart health (cholesterol and triglycerides).

### Bear in mind

The present study suggests that, overall, both Biktarvy and Triumeq are generally well tolerated. Most side effects were mild and temporary.

#### REFERENCE:

Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48-week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet HIV*. 2018; *in press*.

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## D. Biktarvy in women with HIV

Biktarvy is a new regimen in one pill containing the following anti-HIV drugs:

- bictegravir – 50 mg
- TAF (tenofovir alafenamide) – 25 mg
- FTC (emtricitabine) – 200 mg

Of these three drugs, bictegravir is new. It belongs to a class of anti-HIV drugs called integrase inhibitors. Leading treatment guidelines in high-income countries recommend initiating combination treatment with an integrase inhibitor, as these drugs are generally well tolerated and highly effective. Integrase inhibitor combinations are also recommended for second-line use.

In the past eight years, most pivotal (phase III) clinical trials of integrase inhibitors have not had large proportions of HIV-positive women. Pharmaceutical companies have subsequently

conducted trials that enrolled only women who were then given integrase inhibitor-based combination therapy.

In a trial overseen by Gilead Sciences, the manufacturer of Biktarvy, researchers in several countries recruited 470 women who were taking HIV treatment (ART) and whose viral loads were suppressed (less than 50 copies/mL) and randomly assigned them to either continue on their present regimen or to switch to Biktarvy. After 48 weeks the study found that Biktarvy was similarly effective and well tolerated as the women's other regimens. Rates of side effects in women taking Biktarvy were relatively low. There were a small number of pregnancies with no apparent ill effects of Biktarvy on the infant. However, larger studies will be needed before researchers can be certain about the safety of Biktarvy during pregnancy.

### Study details

Researchers in several countries recruited women for this study (the countries are listed in decreasing order of the number of women enrolled):

- Uganda
- Russian Federation
- Thailand
- United States
- Dominican Republic

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

- age – 40 years
- major ethno-racial groups: black – 37%; white – 36%; Asian – 21%; Hispanic – 16%
- CD4+ count – 700 cells/mm<sup>3</sup>
- 90% of women did not have symptoms of HIV disease
- eGFR (estimated glomerular filtration rate; an assessment of overall kidney health) – 100 mL/min

Most participants (95%) were taking one of the following single-tablet regimens:

- Genvoya (elvitegravir + cobicistat + TAF + FTC)
- Stribild (elvitegravir + cobicistat + TDF + FTC)

TDF (tenofovir disoproxil fumarate) is the older formulation of tenofovir that can cause kidney injury and thinner bones in some people. TAF is the newer formulation of tenofovir that is generally safer.

## Results

At the 48th week of the study, the proportions of participants with an undetectable viral load (less than 50 copies/mL) were as follows:

- Biktarvy – 96%
- other regimens – 95%

Statistical analysis found that the effectiveness of Biktarvy was similar to the other regimens. The technical term for this is “non-inferior.”

None of the participants developed resistance to the drugs in Biktarvy.

Three women stopped taking Biktarvy; they left the study and switched to other regimens.

## Adverse events

The term *adverse events* refers to the unfortunate events that can sometimes occur in a clinical trial. Some of these events may be due to drug side effects, some may be caused by the underlying disease process and some may have nothing to do with the clinical trial.

## Pregnancy

According to the study protocol, women who became pregnant while taking Biktarvy were supposed to leave the study and change their regimen to one chosen by their doctor. The other women in the study who were not taking Biktarvy and who became pregnant were given a regimen chosen by the study researchers.

The pregnancies in the study were distributed as follows:

- Biktarvy – five pregnancies (one live birth, two abortions and the outcome of the other two pregnancy outcomes were not yet documented)

- other regimens – seven pregnancies (two live births, two miscarriages, one ongoing pregnancy and two pregnancy outcomes not yet documented)

There were no reported birth defects in either group. However, the study was not designed to assess the safety of Biktarvy during and after pregnancy. Information about Biktarvy’s safety during pregnancy will take many years to accumulate. Such information will be obtained from case reports and other studies.

## Kidneys

There were no significant differences between the regimens when it came to eGFR results. Other, more complex assessments of kidney health showed only modest improvements, particularly in women who had been previously taking the older formulation of tenofovir (TDF) and who switched to TAF (as part of Biktarvy) when they entered the study.

## Other adverse events

Most adverse events reported in the study were of mild to moderate intensity. Adverse events that were judged to be related to the drugs used in the study included the following:

- Biktarvy – two cases each of anemia; two cases of nausea and vomiting; one case each of headache, feeling sleepy during the daytime, diarrhea, type 2 diabetes, pre-diabetes, anxiety, sleeping problems, and an unspecified “emotional disorder”
- other regimens – one case each of higher-than-normal levels of the waste product bilirubin in the blood, depression, and bone/joint pain

There was one death in the study, which occurred in someone who was taking a non-Biktarvy regimen. The death occurred because of complications from a severe flu.

## Bear in mind

The findings from this study suggest that Biktarvy is generally safe in HIV-positive women. However, larger studies are needed to assess the safety of Biktarvy in pregnant women. Information for such studies may take years to accumulate, as Biktarvy is new and HIV-positive women may be cautious

in their use of this single-tablet regimen because of concerns about potential adverse effects on the fetus.

#### REFERENCE:

Kityo C, Hagins D, Koenig K, et al. Switching to bicitegravir/emtricitabine/tenofovir alafenamide in women. *Conference on Retroviruses and Opportunistic Infections*, 4-7 March 2018. Boston, Massachusetts. Abstract 500.

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### E. CDC recommends use of raltegravir (Isentress) for PEP

In cases of possible exposure to HIV, the use of PEP (post-exposure prophylaxis) has been found to greatly reduce the risk of HIV infection. For PEP to work, it must be initiated within 72 hours of exposure and taken every day for 28 consecutive days, exactly as directed. Coverage of PEP varies across and even within some provinces; check with your pharmacist or sexual health clinic for information on subsidized access to PEP in your region.

Until recently, the anti-HIV drug dolutegravir (Tivicay) was commonly used as part of PEP regimens, usually along with the drugs TDF + FTC. However, in May 2018, regulatory agencies in Europe and North America issued cautionary statements about the use of dolutegravir in the first month of pregnancy and its possible association with an increased risk of birth defects. For further information, see the CATIE News story: <http://www.catie.ca/en/catienews/2018-05-24/agencies-issue-caution-about-use-dolutegravir-pregnant-hiv-positive-women>

As a result, many regulatory agencies have suggested that doctors avoid prescribing dolutegravir-containing regimens to HIV-positive women of childbearing potential.

Now the U.S. Centers for Disease Control and Prevention (CDC) has made a statement concerning PEP and dolutegravir. The CDC says that healthcare providers prescribing PEP should avoid the use of dolutegravir for:

- “non-pregnant women of childbearing potential who are sexually active or have been sexually assaulted and who are not using an effective birth control method,” and

- “pregnant women in early pregnancy since the risk of an unborn infant developing a neural tube defect is during the first 28 days.”

The CDC added:

“The preferred regimen for these women is raltegravir (Isentress) + tenofovir + FTC (emtricitabine). However, individual circumstances may dictate consideration of alternatives (eg, should raltegravir be unavailable).”

“The CDC currently recommends that prior to starting PEP all women of childbearing potential should have a pregnancy test performed. If the PEP regimen for a non-pregnant woman of childbearing potential must include dolutegravir, she should use an effective birth control method until the PEP regimen is completed.”

The CDC also reminds healthcare providers that women who do not get sufficient amounts of the B-complex vitamin folic acid are at increased risk for having babies with a type of birth defect called a neural tube defect. The agency stated: “All women who are of childbearing potential, regardless of pregnancy status, should be provided with at least 400 micrograms of folic acid daily.”

#### REFERENCE:

Centers for Disease Control and Prevention. Interim statement regarding potential fetal harm from exposure to dolutegravir – implications for HIV post-exposure prophylaxis (PEP). *Statement*. 23 May 2018.

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### F. FDA warns that Prezcoibix should not be used by HIV-positive pregnant women

Prezcoibix is the brand name of a pill containing the anti-HIV drug darunavir and the boosting agent cobicistat. The purpose of cobicistat is to raise and maintain levels of darunavir so that once-daily dosing can be effective. However, during pregnancy, a woman’s weight increases and the standard dose (or combination) of some anti-HIV drugs may not be sufficient.

In June 2018, the U.S. Food and Drug Administration (FDA) changed the prescribing

information on Prezcoibix. It stated that Prezcoibix should not be used by pregnant women because of “substantially lower exposures of darunavir and cobicistat during pregnancy.”

The FDA also stated that “an alternative regimen is recommended for women who become pregnant during therapy with Prezcoibix.” It did not list a specific alternative regimen.

The recommendation by the FDA is based on data from a study of seven pregnant HIV-positive women who were evaluated during their second and third trimesters as well as 12 weeks after giving birth. Six women completed the study. The FDA reported that the concentrations of darunavir and cobicistat were very low during the second and third trimesters of pregnancy. Furthermore, one woman had virological failure (viral load greater than 1,000 copies/mL) during the third trimester of her pregnancy. The FDA did not release data on the HIV infection status of the infants born to these women.

#### REFERENCE:

Struble K, Thompson E, Stanfield M. Prezcoibix label. *FDA HIV email updates*. 5 June 2018.

## II CO-MORBIDITIES

### A. Issues unrelated to HIV are affecting survival

Since 1996, the availability of potent combination anti-HIV therapy (ART) in Canada and many high-income countries has led to significantly reduced rates of AIDS-related illness and death, at least among people who are aware of their infection and who take ART every day exactly as directed so that the amount of HIV in their blood is suppressed. As a result of sustained use of ART, many HIV-positive people will live into their senior years. Furthermore, clinical trials have shown that HIV-positive people who initiate ART and achieve and maintain an undetectable viral load do not pass on HIV to their sexual partners. However, researchers are increasingly finding that some, perhaps many, HIV-positive people have co-existing health conditions—these are called co-morbidities.

A large observational database called ART-CC (Antiretroviral Therapy Cohort Collaboration) has amassed health-related information from leading clinics in Western Europe and North America. In Canada, clinics in southern Alberta and British Columbia participate in ART-CC. From time to time the researchers involved in ART-CC analyse their data and issue reports.

A recent analysis from ART-CC focused on data from nearly 125,000 HIV-positive people who initiated ART between 1996 and 2014 and were subsequently monitored. The ART-CC researchers sought trends in illnesses both related and unrelated to HIV.

The researchers found that deaths from complications unrelated to AIDS were twice as high as deaths due to AIDS-related complications. Interventions, some of which are discussed later in this report, are needed to prevent deaths from all causes in HIV-positive people.

### Study details

The ART-CC enrolled adults who entered the study upon initiating ART. The present analysis focused on 124,537 participants whose average profile at the start of the study was as follows:

- 76% men, 24% women
- age – 38 years
- CD4+ count – 244 cells/mm<sup>3</sup>
- viral load – 67,000 copies/mL
- the researchers grouped participants based on how they were infected, as follows:
  - heterosexual sex – 35%; gay/bisexual men having sex with other men – 35%; injecting street drugs – 17%; receiving contaminated blood transfusions – 1%; and in the remainder of cases, no information was available as to how HIV infection occurred
- length of time in the study – five years

### Results

About 11% of participants developed an AIDS-related illness. Such illness can occur in the first several months after initiating ART, depending on the degree of weakness of the immune system. ART helps the immune system to begin repairing itself, but these repairs take time.

The researchers focused on three AIDS-related complications because they were interested in finding out more about them. The proportions of participants who developed these complications are as follows:

- TB (tuberculosis) – 15%
- PCP (Pneumocystis pneumonia) – 13%
- NHL (non-Hodgkin’s lymphoma) – 7%

Note that half of the participants had fewer than 245 CD4+ cells when they entered the study. In light of this, it should not be surprising that these complications occurred.

## Deaths

There were 11,280 deaths during the study, which were distributed as follows:

- AIDS related – 24%
- unrelated to AIDS – 36%
- unknown – 40%

Here is the distribution of deaths from causes unrelated to AIDS:

- cancers – 24%
- “accident/suicide/overdose” – 17%
- cardiovascular disease – 16%
- serious infections unrelated to AIDS – 15%
- liver complications – 13%
- lung complications – 3%

## Preventing AIDS-related complications

AIDS-related complications occur because of a weakened immune system. Generally, such complications become an issue when the CD4+ count has fallen below 200 cells/mm<sup>3</sup> or lower. To reduce the risk of people becoming susceptible to AIDS-related infections, the ART-CC researchers recommended that people at risk for HIV be offered the following:

- frequent HIV testing (so that the infection can be diagnosed in the early stages)
- early initiation of ART

## Preventing complications unrelated to HIV

As issues unrelated to AIDS caused many deaths in the study, the researchers called for reducing the factors that increase the risk of death unrelated to AIDS. To do this, screening for at least the following issues would be needed:

- co-infection with hepatitis B and C virus infections
- smoking
- kidney injury
- human papillomavirus-related growths in the ano-genital area and mouth/throat
- cardiovascular disease
- anxiety, depression and other mental health conditions
- excess weight
- problematic substance use
- adherence to HIV treatment

Should screening find these issues, potential interventions could include the following:

- treatment for hepatitis B or hepatitis C virus
- a vaccine is also available for hepatitis B virus for people at risk of this infection
- smoking cessation
- treatment of cardiovascular disease, including advice (via referral to a registered dietitian if available) about healthy eating, an exercise program and the use of medication to help normalize blood pressure and lipid levels in the blood
- referral to alcohol or harm reduction and drug treatment programs

The ART-CC does not collect information about substance use, mental health and body mass index (BMI). Also, 40% of the causes of death were missing from the present analysis, as this data had not been supplied by the clinics that participate in the ART-CC. However, researchers performed a sensitivity analysis, removing clinics that did not send sufficient data, and found that the overall trends discerned in the larger analysis were still present. This suggests that health problems unrelated to AIDS will become even more of an issue for HIV-positive people over time. If the full benefits of ART—near-normal life expectancy—are to be experienced by more people, attention must be paid to factors that appear to be increasingly affecting HIV-positive people and their survival. By

screening for and treating these conditions, quality of life can also be maintained or even improved.

#### REFERENCE:

Pettit AC, Giganti MJ, Ingle SM, et al. Increased non-AIDS mortality among persons with AIDS-defining events after antiretroviral therapy initiation. *Journal of the International AIDS Society*. 2018 Jan;21(1).

## B. Co-morbidities in selected Canadian clinics

As all people age they become at risk for developing illness related to the decline of important organ-systems. Some people with HIV appear to be at heightened risk for such illnesses, called co-morbidities. If left untreated, co-morbidities can degrade health-related quality of life and likely shorten life expectancy.

Researchers at five HIV clinics in four provinces—British Columbia, Saskatchewan, Ontario and Quebec—collaborated on a study to review data collected from 1,000 HIV-positive people who had recently made a clinic visit.

Analysis of the data revealed that co-morbidities were common. Furthermore, nearly 75% of participants had two or more co-morbidities.

The study underscores the importance of screening for and, when necessary, offering treatment for co-morbidities.

### Study details

The study was retrospective in design; that is, it reviewed data already collected for another purpose and then analysed that data.

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

- 82% men, 18% women
- age – 52 years
- time since HIV diagnosis – 14 years
- major ethno-racial groups: white – 74%; Indigenous – 12%; black – 9%; Asian – 2%; Hispanic 2%
- currently using substances: tobacco – 37%; alcohol – 55%; recreational drugs – 37%; injecting street drugs – 13%

- CD4+ cell count – 560 cells/mm<sup>3</sup>
- viral load – less than 40 copies/mL
- eGFR (estimated glomerular filtration rate; a routine measure of kidney health) – 77 mL/minute
- hepatitis C virus co-infection – 28%

### Results

The distribution of co-morbidities among participants was as follows:

- brain related – 53%
- liver related – 50%
- overweight/obesity – 43%
- abnormal levels of fatty substances (cholesterol, triglycerides) – 37%
- thinner-than-normal bones – 24%
- higher-than-normal blood pressure – 24%
- kidney injury/dysfunction – 18%
- cardiovascular disease – 15%
- type 2 diabetes – 9%

Only 7% of participants did not have a diagnosis of a co-morbidity.

The researchers found that almost 75% of participants had two or more co-morbidities:

- having two co-morbidities – 26%
- having three co-morbidities – 18%
- having four or more co-morbidities – 30%

### Bones

Bone mineral density tends to generally decline with age and thinner bones are more susceptible to fractures. Studies with HIV-positive people have found that thinner-than-normal bones are relatively common.

Researchers examined data from a subset of 199 participants in the present study who had bone density scan data and found the following:

- 29% had normal bone density
- 58% had moderately thin bones (osteopenia)
- 13% had severely thin bones (osteoporosis)

### Heart and kidney disease

The kidneys are rich in blood vessels, as these organs filter the blood, so conditions that affect the heart and blood vessels tend to also affect

the health of the kidneys. Researchers used risk calculators that could estimate the risk for differing degrees of heart and kidney disease and found the distribution of these risks as follows:

Cardiovascular disease risk

- low – 58%
- medium – 38%
- high – 10%

Kidney disease risk

- low – 12%
- medium – 19%
- high – 69%

### Bear in mind

In a sample of 1,000 HIV-positive Canadians taking ART, researchers found a high level of co-morbidities. Furthermore, a significant proportion of participants (nearly 70%) were at elevated risk for kidney disease and 10% were at elevated risk for cardiovascular disease.

The present study's design was retrospective in nature and participants were not apparently chosen at random. Retrospective studies cost less than other study designs, as the work of capturing the data has already been done, and they are a good first step at exploring an issue. However, analyses of retrospective studies can sometimes inadvertently give rise to biased conclusions. Nonetheless, the research team documented the issues that were affecting patients who recently visited their doctor, and this is useful.

A different approach might have been to also assess HIV-negative people of the same age, gender and socio-economic status and compare the proportions of co-morbidities. However, such an approach would have cost much more money, been labour-intensive and taken much more time to capture data, as physicians do not normally engage with socio-economic data at the level of the individual. Different study designs have advantages and disadvantages, and these must be considered in light of available funding.

The study is important because among people whose viral loads are suppressed due to ART, co-morbidities and their risk factors are major drivers of poor health-related quality of life. If they are left untreated, co-morbidities can affect life expectancy.

### For the future

The study has expanded to include data from 10 clinics, for a total of 2,000 people, and data from this larger sample is being analysed. This expanded data set would provide a good picture of common co-morbidities affecting HIV-positive people in Canada. The researchers hope to present the results of the expanded data set at a conference in 2019. The results of the final data set will be very useful and provide a rationale for other studies that monitor the health of HIV-positive people as well as interventions to help maintain or improve their health by reducing the risk or severity of co-morbidities.

### REFERENCE:

Fraser C, Wong A, Baril J-G, et al. Canadian HIV practice reflective initiative to improve management of patients with co-morbidities. *Canadian Association for HIV Research*, 26-29 April 2018, Vancouver, British Columbia. Poster CSP8.10.

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### C. Pilot study finds intense exercise is good for older HIV-positive men

On average, HIV-positive adults appear to be at increased risk for aging-related complications. One potential strategy to reduce this risk is to engage in regular exercise. However, such a strategy has not been tested in older HIV-positive people.

Researchers at the University of Maryland in the U.S. conducted a randomized pilot study of high-intensity vs. moderate-intensity exercise in 22 older HIV-positive men. The exercise was done under supervision at the same athletic facility three times weekly for 16 consecutive weeks. All participants were relatively healthy and taking HIV treatment (ART).

The body's ability to maximize its use of oxygen is called V02 max for short. Sports exercise specialists generally consider V02 max to be a good indicator of cardiovascular fitness.

In the study, the men who engaged in high-intensity aerobic exercise (but not moderate intensity) showed a significantly increased V02 max. Also, the endurance of all the men increased, more so those who underwent intensive exercise. The improved ability of the men to use oxygen may have clinical implications, discussed later in this report.

As the study was small, conclusions affecting the average HIV-positive person in the community cannot be drawn from it. However, the results pave the way for a larger study of exercise in HIV-positive people, looking at its many benefits, particularly in older people. The results of a larger study can be generalized to more HIV-positive people.

### Study details

Researchers enrolled relatively healthy volunteers who did not have any of the following health issues:

- higher-than-normal blood pressure (hypertension) that was untreated
- heart pain
- anemia

Eleven participants were assigned to each of the study interventions.

The average profile of participants was as follows:

- age – 57 years
- CD4+ count – 475 cells/mm<sup>3</sup>
- undetectable viral load – 94%
- at least one-third of participants had co-existing conditions, such as treated hypertension, type 2 diabetes and hepatitis C virus infection (one-third of participants also had a history of injecting street drugs)
- 75% of participants smoked

### Monitoring

Participants underwent extensive monitoring during the study, particularly when exercising, including heart rate, blood pressure, oxygen consumption and carbon dioxide production.

Participants who engaged in high-intensity exercise did so on a treadmill. If they encountered joint pain, they had the option of doing their exercise on an elliptical machine, which has a low impact on joints. Participants who did moderate-intensity exercise walked around a standard running/walking track.

At first, participants underwent exercise training for between 20 and 30 minutes; this was gradually increased by about 10% each week. Toward the end of the study, participants were exercising for about 40 minutes per session.

Participants also received dietary counselling so that their weight remained stable during the study.

### Results—At the end of the study

In the men who did high-intensity exercise, the following changes were found:

- the ability of the body's muscles to use oxygen increased significantly
- endurance increased by 27%
- levels of HDL-C (so called “good cholesterol”) increased significantly

Among the men who engaged in moderate-intensity exercise, the following changes were noted:

- no significant increase in the ability of the body's muscles to use oxygen occurred
- endurance increased by 11%
- levels of HDL-C fell modestly

### Dropouts

Six participants (four doing moderate-intensity exercise and two doing high-intensity exercise) prematurely left the study for the following reasons:

- osteoarthritis – two people
- stroke – one person
- communication ceased with the study clinic – three people

### Bear in mind

This was a pilot study, so its results are not broadly generalizable. However, it is a good first step and provides a rationale for a larger and possibly longer study on exercise in HIV-positive men.

The researchers found an increase in VO<sub>2</sub> max in participants who underwent high-intensity exercise. They stated that “in the general geriatric population” an increase of similar magnitude over a decade is associated with the following:

- 15% reduced risk of dying from all causes
- 19% reduced risk of dying from complications of cardiovascular disease

However, the present study cannot draw firm conclusions about the health benefits of exercise

in older HIV-positive people because it is too small. A larger, longer study is needed for such a purpose.

Other studies have found that HIV-positive people have increased levels of inflammation. This is partially reduced by initiating ART and maintaining an undetectable viral load. However, residual inflammation remains and some researchers are concerned that this heightened inflammation may make some HIV-positive people more susceptible to a range of chronic conditions, including inflammatory disorders. A longer study of high- vs. low-intensity exercise in HIV-positive people could explore the impact of exercise on the following issues:

- inflammation
- mood
- blood sugar
- lipid levels in the blood
- cognitive functioning
- health-related quality of life

### **CATIE Resources**

Exploring HIV and inflammation –  
*TreatmentUpdate 223*

Exercise—Potential impact on inflammation and mood – *TreatmentUpdate 205*

Healthy Living – *A practical guide to a healthy body for people living with HIV*

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  2. Quigley A, O'Brien K, Parker R, et al. Exercise and cognitive function in people living with HIV: a scoping review. *Disability and Rehabilitation*. 2018 Jan 29:1-12.
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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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CATIE is Canada's source for up-to-date, unbiased information about HIV and hepatitis C. We connect people living with HIV or hepatitis C, at-risk communities, healthcare providers and community organizations with the knowledge, resources and expertise to reduce transmission and improve quality of life.

For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients' needs.

CATIE provides such information through a comprehensive website ([www.catie.ca](http://www.catie.ca)), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

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#### *HepCInfo Updates*

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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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