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I ANTI-HIV AGENTS

A. Doravirine begins to be listed on formularies

Doravirine is available as a pill and sold under the brand name Pifeltro. It belongs to the class of anti-HIV drugs called non-nukes (NNRTIs). Doravirine is also available in a pill called Delstrigo, a complete treatment for HIV that contains the following medicines:

- doravirine
- TDF (tenofovir disoproxil fumarate)
- 3TC

Both formulations of doravirine are taken once daily with or without food. In clinical trials doravirine was generally well tolerated and an effective part of HIV treatment.

About a year ago both formulations of doravirine were approved by Health Canada. Negotiations between the manufacturer of doravirine (Merck) and Canada's provinces and territories about the discount they receive when purchasing doravirine have recently been finalized. As a result, doravirine (including Delstrigo) will be covered under the list of medicines that the province of Ontario subsidizes. Each province or territory has its own list of subsidized medicines, which is called a formulary. Over the coming weeks and months, more of Canada's provinces and territories will add doravirine (and Delstrigo) to their formularies. To find out when doravirine is on a specific region's formulary, contact your local pharmacist.

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Resources

Pifeltro (doravirine) – *CATIE Factsheet*

Delstrigo – *CATIE Factsheet*

B. The debut of fostemsavir

Fostemsavir is a drug that has completed phase III clinical trials. It is intended for use by people who have strains of HIV that are resistant to many classes of anti-HIV drugs.

Fostemsavir is the first of a new class of drugs called attachment inhibitors. It works by binding to an HIV protein called gp120 found on the surface of HIV. The virus uses gp120 to help attach itself to a cell and then infect the cell. By binding to gp120, fostemsavir prevents HIV from infecting cells.

Subtypes of HIV

There are many major strains, or subtypes, of HIV. Laboratory experiments have found that fostemsavir is active against most strains of HIV that are commonly found in North America, Western Europe, East Asia, Australia and New Zealand.

However, fostemsavir is not active against a subtype of HIV called Group O (Outlier). This strain is concentrated in parts of West-Central Africa and is not commonly distributed. Fostemsavir is not active against HIV-2. This strain of HIV is commonly found in West Africa.

Fostemsavir is active against strains of HIV-1 that are resistant to other treatments, including the following drugs that work as receptor or fusion inhibitors:

- T-20, enfuvirtide (Fuzeon)
- maraviroc (Celsentri)
- Ibalizumab (Trogarzo)

A prodrug

Fostemsavir is called a “prodrug” by chemists. When a fostemsavir pill is swallowed and the drug is absorbed in the intestines, it is converted into its active form—temsavir. It is this active form (temsavir) that has antiviral activity. Prodrugs are

often developed to help overcome absorption problems with the original formulation of the drug.

In clinical trials

The dose of fostemsavir that was used in the phase III clinical trial was 600 mg twice daily, together with other anti-HIV drugs. In phase II and III clinical trials, the most common side effects that were considered generally mild were headache and rash.

Adverse effects of moderate to severe intensity occurred in 18% of participants and were as follows:

- diarrhea
- headache
- nausea
- vomiting
- weakness or lack of energy

Note that people who enrolled in clinical trials of fostemsavir were not in general good health because their pre-study regimens had been failing. On average, people in the phase III study had CD4+ counts below the 100 cell/mm³ mark. Such people could be experiencing low-grade and other infections that accompany a low CD4+ cell count. However, it is likely that some of the adverse effects listed previously are side effects of fostemsavir and/or some of the other medicines that people in the study took.

Opioid use

Fostemsavir, taken at a dose of 600 mg twice daily, has been studied in 32 HIV-negative people (72% men, 28% women) who were being treated for substance dependency with stable doses of the following opioid substitution medicines:

- methadone (between 40-120 mg) – 16 participants
- a combination of buprenorphine (between 8–24 mg) and naloxone (between 2–6 mg) – 16 participants

According to the scientists monitoring the study, over the course of 10 days “there were no deaths, serious adverse events or adverse events leading to discontinuation of study therapy.”

Methadone or a combination of buprenorphine and naloxone did not reduce the concentration of fostemsavir in the blood.

Next in *TreatmentUpdate* we discuss results from the phase III trial of fostemsavir.

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5. Lataillade M, Zhou N, Joshi SR, et al. Viral drug resistance through 48 weeks, in a phase 2b, randomized, controlled trial of the HIV-1 attachment inhibitor prodrug, fostemsavir. *Journal of Acquired Immune Deficiency Syndromes*. 2018 Mar 1; 77(3):299-307.

C. Fostemsavir in treatment-experienced people

HIV-positive people who doctors described as “heavily treatment-experienced” were enrolled in a study on fostemsavir called Brighte. Most participants had strains of HIV that were resistant to multiple classes of drugs and their pre-study regimens were failing.

When used as part of combination HIV treatment, fostemsavir can be highly effective against HIV. As is generally the case with other anti-HIV drugs, the more active drugs in a regimen, the more effective the regimen. In Brighte, fostemsavir was able to stabilize and/or improve the health of many participants.

Study details

People enrolled in Brighte were initially divided into the following two groups:

Randomized group

In this group, participants were randomly assigned to receive one of the following regimens:

- fostemsavir 600 mg twice daily + their pre-study regimen for eight consecutive days – 203 people
- placebo + pre-study regimen for eight consecutive days – 69 people

After this initial period in the study, all of the above participants received fostemsavir + an optimized background regimen (OBR). To determine each participant’s OBR, doctors used the results of HIV resistance testing to try and find drugs to which HIV was fully susceptible.

Non-randomized group

These 99 participants enrolled in the study had pre-study regimens that were failing; laboratory analysis revealed that their HIV was resistant to all approved HIV treatments. They received fostemsavir at 600 mg twice daily + an optimized background regimen. However, in their case, due to previous extensive drug resistance by HIV, this OBR was only partially effective against HIV. The study scientists hoped that even low-level anti-HIV activity from some drugs in the OBR, combined with fostemsavir, could extend the survival of some of these participants.

The average profile of all participants who entered the study was as follows:

- age – 50 years
- 78% men, 22% women
- major ethno-racial groups: white – 70%; black – 22%
- viral load – 4.6 log (about 30,000 copies/mL)
- CD4+ count – 80 cells/mm³

Commonly used anti-HIV drugs in the OBR:

- dolutegravir (Tivicay and in Triumeq)
- darunavir
- tenofovir DF

Results

The proportions of participants in the randomized group with a suppressed viral load (in this study it was set at 40 copies/mL) at different time points were as follows:

- week 24 – 53%
- week 48 – 54%
- week 96 – 60%

The proportions of participants in the non-randomized group with a viral load less than 40 copies/mL at different time points were as follows:

- week 24 – 37%
- week 48 – 38%
- week 96 – 37%

CD4+ cell counts

The CD4+ cell count is generally used to assess the health of the immune system.

Increases in CD4+ cell counts were generally steady over the course of the study, with the average increases as follows:

- randomized group – 205 additional CD4+ cells/mm³
- non-randomized group – 119 additional CD4+ cells/mm³

As people in the non-randomized group were generally sicker and had fewer treatment options, their increases in CD4+ cell counts were less than those in the randomized group.

Among 71 people who entered the study with less than 50 CD4+ cells (in the randomized group), 56% had a CD4+ count of at least 200 cells/mm³ by week 96.

Another way to assess the immunological health of people is to examine the ratio of CD4/CD8 cells. A ratio less than 1.0 suggests immunological dysfunction and weakness.

Among participants randomized to receive fostemsavir, the ratio was initially 0.2. However, by week 96 it had increased to 0.443, suggesting some improvement in immunological health.

No CD4/CD8 ratios were released by the researchers for the non-randomized group of people.

Safety

The proportions of participants who developed drug-related side effects that were at least of moderate severity were as follows:

- randomized group – 21%
- non-randomized group – 22%

Common drug-related side effects of moderate to severe intensity were distributed as follows:

Diarrhea

- randomized group – 2%
- non-randomized group – 3%

Headache

- randomized group – 2%
- non-randomized group – 1%

Nausea

- randomized group – 3%
- non-randomized group – 5%

Weakness

- randomized group – less than 1%
- non-randomized group – 2%

Serious drug-related side effects were distributed as follows:

- randomized group – 3%
- non-randomized group – 3%

There was a total of 16 serious side effects related to fostemsavir and/or other medicines. These serious side effects were distributed among 12 participants, as follows:

- kidney stones – 2 people
- acute kidney injury – 1 person
- kidney impairment – 1 person
- higher-than-normal levels of blood sugar – 1 person
- higher-than-normal levels of potassium in the blood – 1 person
- immune reconstitution inflammatory syndrome (IRIS) – 3 people
- loss of consciousness – 1 person
- inflammation of the heart – 1 person
- liver injury – 1 person

- muscle weakness – 1 person
- a fetus stopped growing – 1 person
- disorientation – 1 person
- rash – 1 person

The following numbers of people left the study because of adverse events:

Abdominal pain

- randomized group – 2 people
- non-randomized group – 0 people

Chest pain unrelated to the heart

- randomized group – 1 person
- non-randomized group – 1 person

Liver failure

- randomized group – 0 people
- non-randomized group – 2 people

Bear in mind that the population enrolled in *Brighte* was generally unwell. Since the average CD4+ count upon study entry was around 80 cells/mm³, it is likely that many participants would have had symptoms related to uncontrolled HIV and some participants would likely have had low-level (smouldering) AIDS-related infections and tumours. Furthermore, people with low CD4+ cell counts tend to be more susceptible to drug-related side effects.

Fostemsavir helped many people in the study get better. However, for some participants, fostemsavir was the only drug in their regimen that was fully active against HIV. In effect, these people would have been taking fostemsavir monotherapy (equivalent to taking fostemsavir alone). It was therefore inevitable for HIV to develop resistance to fostemsavir in such cases. Once HIV overcame fostemsavir, these participants would have had no future options for treatment and their health would have significantly deteriorated. It should not be surprising then that 29 people died during the study, distributed as follows:

- randomized group – 12 people (4%)
- non-randomized group – 17 people (17%)

A majority of deaths (62%) in the study were due to AIDS-related infections and cancers.

Key points

- When used as part of an optimized background treatment, fostemsavir had good antiviral activity against HIV.
- CD4+ counts and CD4/CD8 ratios improved over the course of the study.
- Fostemsavir was generally safe but because many people in the study were weak and ill, side effects were common. However, serious side effects were not common.

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D. Fostemsavir compassionate access program

ViiV Healthcare has built at least one manufacturing facility to make fostemsavir. The factory should have some supplies of fostemsavir available toward the end of 2019. Sometime in late 2020, fostemsavir should be licensed for use in Canada, the European Union and the United States.

ViiV has stated that it plans to make fostemsavir available on a compassionate access basis for selected patients around the end of 2019. The compassionate access program in Canada will involve a three-stage process that includes the following:

- An application to ViiV by the doctor asking for fostemsavir and explaining the reasons why the patient needs the drug. ViiV will review each application on a case-by-case basis, as currently there is a limited supply of the drug.
- If ViiV approves the application, the next step is for the doctor to apply to Health Canada's Special Access Program (SAP) to seek approval for their patient to get a non-approved treatment (fostemsavir). This process is independent of ViiV.
- Finally, once Health Canada has approved the individual use of fostemsavir via the SAP, ViiV will then contact its factory to have the drug shipped.

Doctors can contact ViiV’s medical department to find out more about the compassionate access program.

II HEALTHY LIVING

A Exercise as medicine

The widespread availability of potent HIV treatment (ART) in Canada and other high-income countries has largely transformed HIV infection into a chronic condition. The benefits of ART are so profound that scientists and doctors increasingly expect that many ART users will have a near-normal life expectancy.

As people with HIV age, issues associated with growing older will become the focus of their overall care and treatment. Such issues can include higher-than-normal blood pressure, excessive weight, pre-diabetes and type 2 diabetes, cardiovascular disease and so on. Some researchers in Canada propose that by helping people engage in more healthy behaviours, particularly exercise, they can help prevent or minimize the impact of some conditions associated with aging. These researchers have formulated evidence-based recommendations for the type and amount of exercise that can be prescribed for HIV-positive people.

Evidence-based findings and recommendations

Studies have generally found a relatively low rate of physical activity (exercise is a subset of this) among HIV-positive people. To help remedy this situation, a team of scientists in Canada and the U.S. collaborated to review exercise-related studies with HIV-positive people over the past decade. After reviewing the studies, the scientists developed recommendations to help healthcare providers and counsellors “prescribe and support physical activity engagement” among HIV-positive people.

These recommendations are important because studies suggest that issues such as being overweight and obese are more common in the average HIV-positive person today than they were earlier on in the pandemic. A future issue of *TreatmentUpdate* will delve into studies about factors affecting body weight and report on trends in body weight and

obesity among HIV-positive people over the past four decades.

How much and what kind of exercise?

The team of scientists noted that the U.S. Department of Health and Human Services (DHHS) has proposed “that adults—even those with chronic conditions and disability—engage in 150 to 300 minutes of moderate-intensity exercise or 75 to 150 minutes of vigorous-intensity aerobic physical activity each week.”

The scientists stated that “for sedentary or physically inactive [HIV-positive people], prescribing movement breaks or walking may be a practical strategy to increase physical activity, as it does not require special skills or equipment.”

Additionally, the scientists noted that the DHHS recommends the following measures:

- “muscle-strengthening activity on two or more days per week”
- “balance training...as part of older adults’ weekly physical activity to reduce fall risk”
- “moving more and sitting less will benefit nearly everyone”

The team of scientists stated that “although some people with HIV may have unique physical limitations that must be accommodated in order for them to safely engage in physical activity, the take-home recommendation is that physical activity participation is key to maximizing health and function.”

Types of physical activity

The scientists pointed out that in addition to traditional aerobic (walking, biking and swimming) and resistance (weight-bearing) exercises, there is “lower-intensity physical activity” that can be considered, such as the following:

- yoga – the team noted that among HIV-positive people, yoga is associated with the following benefits: “improvement in quality of life; reduction in depressive symptoms and reduction of blood pressure”
- Tai Chi – according to the scientists, this form of activity “was associated with improved

[sense of] wellbeing and balance” in HIV-positive people

Intensity of activity

The scientists stated that studies with HIV-positive people have found that “high-intensity aerobic and resistance exercise (based on target heart rate and resistance load) improved endurance and strength to a similar, if not greater, extent than moderate-intensity exercise.” Such gains were also found among older HIV-positive people.

Taking this and other exercise-related findings into account, the scientists made the following statement:

“These studies of high-intensity exercise have indicated no reason to dissuade [HIV-positive people]—young or old—from progressing to high-intensity exercise, following several weeks of moderate-intensity exercise training.”

Identifying and overcoming barriers

Intrapersonal barriers

The scientists reviewed many studies and found that there were “intrapersonal barriers” to engagement in exercise, including the following:

- “worries about HIV disclosure and stigma”
- “a lack of social support”

However, they found that there was at least one study in which “participants found the [exercise environment] less stigmatizing than they initially feared.”

The researchers also stated that “health care providers’ recommendations can also play a key role in perceptions and engagement in physical activity [among HIV-positive people].”

Environmental barriers

The scientists stated that there may also be “environmental barriers” to physical activity among HIV-positive people, including the following:

- “concerns about physical safety”
- “physical and financial accessibility”

They encouraged healthcare providers and community workers to take such issues into

account when developing “a physical activity plan” for HIV-positive people. One potential solution from the scientists to help overcome environmental barriers is to encourage HIV-positive people to walk “in a shopping mall or to engage in short bouts of physical activity throughout the day that do not require gym access or equipment.” (Note that some gyms and community organizations offer subsidized access to athletic facilities.)

Changing behaviours

The researchers encouraged primary care providers to periodically “enquire about and promote physical activity among [HIV-positive people].”

One strategy they suggested for helping HIV-positive people engage in more physical activity is for healthcare providers to collaborate with patients to jointly develop a “physical activity prescription.” The scientists pointed out the non-profit website Exercise is Medicine (<https://exerciseismedicine.org/>), which can be very useful for healthcare providers and has suggestions for effecting simple behavioural changes.

Based on studies, the scientists recommended that the following behaviour change strategies be adopted:

Self monitoring

This can be done with wearable technology such as a pedometer, Fitbit, smartphone apps or online tools (the scientists recommended <https://go4lifemia.nih.gov/> from the U.S. National Institutes of Health) or simply pen and paper.

Goal setting and action planning

The scientists stated that “goal setting encourages specific behaviour resolution (eg. engaging in more physical activity this week), while action planning involves detailed planning of what the person will do, when they will engage in the specified behaviour and for how long.”

Prompts, cues and scheduling

Prompts can be used to remind people to engage in physical activity. The scientists stated that these reminders “may drive habit formation and improve long-term physical activity adherence.” They also said that “a calendar, alarms...cell phone reminders” can be used to set aside time for physical activity. They found research that suggested that “pre-

scheduled activity is often more adhered to than relying on impromptu self-motivation.”

Social support

The research team stated that there is evidence for the “prominent role that healthcare providers have in integrating health promotion into routine HIV care. Thus, providers can leverage their strong patient relationships to emphasize a holistic concept of well-being that includes physical activity. Persons are more likely to engage in physical activity if they are linked to a similarly motivated person with whom they are able to engage in physical activity, creating a ‘buddy system’... In addition, the social environment of group exercise can enhance motivation and adherence to physical activity among older [HIV-positive people].”

Bear in mind

The team of scientists has put forward a set of useful, evidence-informed and practical recommendations for increasing physical activity among HIV-positive people. Hopefully these recommendations will be increasingly implemented over the coming years.

Resources

Pilot study finds intense exercise is good for older HIV-positive men – *TreatmentUpdate* 228

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

Exercise and the brain – *TreatmentUpdate* 203

Exercise found to improve memory – *TreatmentUpdate* 186

REFERENCE:

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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), 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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