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## I COMPLICATIONS

### A. Challenges in achieving a longer life

The widespread use of potent combination anti-HIV therapy (commonly called ART) has led to dramatic declines in deaths due to AIDS-related complications across Canada and other high-income countries. Researchers expect that many HIV-positive people who take ART every day exactly as directed will likely have a near-normal lifespan.

What are the factors that can diminish survival among ART users today? To answer this question, researchers with the U.S. health maintenance organization Kaiser Permanente in California reviewed and compared health-related data from nearly 300,000 people. They found that certain factors played an important role in reducing survival among HIV-positive people, including the following—co-infection with hepatitis-causing viruses, excessive intake of alcohol, substance use and tobacco smoking.

If HIV-positive people are to survive well into their senior years, doctors and nurses need to screen HIV-positive people for these issues. Importantly, the biological and psychological drivers of engagement in substance use also need to be addressed.

### Study details

The Kaiser researchers amassed data between 1996 and 2011 on 24,768 HIV-positive people. In their database, they matched each HIV-positive person to data from about 10 other HIV-negative people of similar characteristics (such as age and gender).

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The average profile of HIV-positive people upon entering the study was as follows:

- age – 41 years
- 91% men, 9% women
- major ethno-racial groups – 56% white, 21% black and 18% Hispanic
- main demographic groups – 76% men who had sex with men, 16% men who had sex with women, 7% sharing equipment for injecting street drugs
- a positive test for hepatitis B virus (HBV) or hepatitis C virus (HCV) – 12%
- ever engaged in drug or alcohol abuse – 21%
- ever smoked – 45%
- 46% were taking ART
- 40% initiated ART during the course of the study

## Results

In the case of HIV-positive people, as with reports from other high-income regions, the Kaiser researchers found that, as of 1996, death rates decreased and life expectancy began to increase.

The researchers performed calculations (in a manner similar to what life insurance companies do) to estimate life expectancy for a typical 20 year old at different points in time and arrived at the following results:

In 1996

- An HIV-negative 20 year old could expect to live an additional 63 years, for a total life expectancy of 83 years.
- An HIV-positive 20 year old could expect to live an additional 19 years, for a total life expectancy of 39 years.

In 2011

- An HIV-negative 20 year old could expect to live an additional 65 years, for a total life expectancy of 85 years.
- An HIV-positive 20 year old could expect to live an additional 53 years, for a total life expectancy of 73 years.

## The gap in time

When one subtracts the differences in life expectancy between an HIV-negative person and an HIV-positive person in 2011, there is a gap of 12 years. In sub-analyses, researchers found that gaps

in life expectancy existed regardless of gender, race/ethnicity or HIV risk group.

## Optimal treatment

Other recent research has shown that starting ART when the CD4+ count is relatively high confers many health benefits. It is possible that people who have initiated ART in recent years at higher CD4+ counts may perhaps be somewhat healthier than people who initiated ART with older drugs further in the course of HIV disease. That is, people who initiated ART in the recent era are likely to have less injury to their immune system. To take this into account and reduce potential unintended bias, the Kaiser researchers decided to perform a sub-analysis by focusing on the most recent data, the years 2008 to 2011. They found that when participants initiated ART at CD4+ counts of 500 cells/mm<sup>3</sup> or greater, the gap in life expectancy between them and their HIV-negative counterparts was about eight years.

When focusing on participants in this time period who initiated ART when their CD4+ count was at least 500 cells/mm<sup>3</sup>, researchers found the following:

- participants who did not have HBV or HCV – the gap was 7.2 years
- participants who did not have drug or alcohol abuse issues – the gap was 6.6 years
- participants who did not smoke – the gap was 5.4 years

Based on these results, the researchers encouraged doctors and nurses to offer screening, treatment and counselling for the issues that can reduce life expectancy among HIV-positive patients. By making these interventions, doctors and nurses can help improve the lifespan and likely the quality of life of their patients.

There is still a gap in life expectancy calculations using data from up to 2011. However, in a few years the Kaiser database should have accumulated sufficient information from more recent years and a re-analysis of life expectancy should be done to see if gaps still exist.

## REFERENCE:

Marcus JL, Chao C, Leyden W, et al. Narrowing the gap in life expectancy for HIV+ compared with HIV-negative individuals. *Conference on Retroviruses and Opportunistic Infections*, 22–25 February 2016, Boston, MA. Abstract 54

## B. Emerging issues in older HIV-positive people

As people age they become at heightened risk for many health issues. As HIV-positive people survive longer, preventing and treating age-related health issues will become more important.

Researchers at major medical centres in France compared health-related information from more than 13,000 HIV-positive people, some of whom were more than 75 years old. They found that some older people had a statistically significant increase in many age-related complications, in some cases, multiple complications. Consequently, the researchers called for programs to screen HIV-positive people for these conditions so they can be prevented and treated in their early stages. They also recommended collaboration among specialists caring for this population.

### Study details

Researchers extracted information from a database called Dat'AIDS, which has enrolled nearly 44,000 HIV-positive participants, and selected two groups that they described as follows:

- “elderly” (aged 50 to 75 years) – 12,748 participants
- “geriatric” (aged 75 years and older) – 654 participants

The average profile of the elderly participants upon entering Dat'AIDS was as follows:

- age – 56 years
- 75% men, 25% women
- co-infected with hepatitis C virus – 25%
- co-infected with cytomegalovirus (CMV) – 87%
- current smoker – 37%
- engaged in alcohol abuse – 13%
- current or past injection of street drugs – 21%
- current CD4+ count – 560 cells/mm<sup>3</sup>
- 89% had a viral load less than 50 copies/mL
- age at ART initiation – 44 years

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

- age – 78 years
- 72% men, 28% women
- co-infected with hepatitis C virus – 9%

- co-infected with cytomegalovirus (CMV) – 95%
- current smoker – 5%
- alcohol abuse – 13%
- current or past injection of street drugs – 2%
- current CD4+ count – 494 cells/mm<sup>3</sup>
- 89% had a viral load less than 50 copies/mL
- age at ART initiation – 65 years

### Results

The distribution of age-associated illnesses between the two groups of participants was as follows:

#### Type 2 diabetes

- elderly – 11%
- geriatric – 22%

#### Higher-than-normal blood pressure

- elderly – 21%
- geriatric – 42%

#### Cardiovascular disease (except stroke)

- elderly – 9%
- geriatric – 21%

#### Stroke

- elderly – 3%
- geriatric – 6%

#### Cancer (unrelated to HIV infection)

- elderly – 12%
- geriatric – 23%

#### Severe kidney dysfunction

- elderly – 5%
- geriatric – 14%

#### Liver injury arising from hepatitis

- elderly – 5%
- geriatric – 2%

#### Depression

- elderly – 17%
- geriatric – 15%

Readers can see that nearly all conditions were more common in geriatric people, with the exception of depression and liver injury.

The proportion of participants having two or more age-related complications was increased among the geriatric participants as follows:

One age-related condition

- elderly – 71%
- geriatric – 46%

Two or three age-related conditions

- elderly – 25%
- geriatric – 40%

Four or more age-related conditions

- elderly – 4%
- geriatric – 15%

### **Bear in mind**

In both groups of participants, there were high rates of what researchers call “virological success”—having a viral load less than 50 copies/mL because of ART. Furthermore, CD4+ cell counts were around 500 cells/mm<sup>3</sup> in both sets of participants.

However, people aged 76 and older were more likely to have age-related health issues.

The researchers recommended that clinics prioritize screening for and treatment of age-related conditions, especially those that affect the following organ-systems:

- heart and circulatory system
- liver
- kidneys
- bones
- brain

The researchers also cautioned doctors to be aware of the potential for older patients taking multiple medicines, as this may cause unexpected interactions.

The researchers encouraged doctors and nurses to incorporate assessments of geriatric conditions and, when necessary, interventions for those conditions into regular care.

They also would like to see more collaboration among HIV specialists, family doctors and geriatric specialists to help deal with the issue of age-related conditions among aging HIV-positive patients.

### **REFERENCE**

Allavena C, Bernaud C, Lariven S, et al. Aging with HIV: emerging importance of chronic comorbidities in patients over 75. *Conference on Retroviruses and Opportunistic Infections*, 22–25 February 2016, Boston, MA. Abstract 709.

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### **C. Large study looks at risk factors for bone problems in HIV**

Multiple studies have found that HIV-positive people are at increased risk for developing osteopenia and osteoporosis (thinner-than-normal bones) and, in rare cases, osteonecrosis (the degeneration and death of bones, particularly joints). These complications increase the risk for fractures.

Researchers with a large database called EuroSIDA reviewed the health-related data that they had accumulated since 2004. They focused on 11,820 HIV-positive participants who had been monitored for an average of seven years. When it came to fractures and osteonecrosis, the following had occurred:

- 416 people developed 619 new fractures
- 73 people developed 89 new instances of osteonecrosis

Common locations of fractures were as follows:

- arms
- ribs
- feet

### **An immunological link**

In general, the risk of a fracture was greatest among participants with a CD4+ count of 200 cells/mm<sup>3</sup> or less. Fracture risk was much lower among people with a CD4+ count between 501 and 750 cells/mm<sup>3</sup> and lowest among people whose CD4+ count was greater than 750 cells/mm<sup>3</sup>.

There was no similar trend between CD4+ cell counts and the risk of osteonecrosis.

## Risk factors for fractures

Among the 619 new fractures, the risk factors that researchers uncovered were as follows:

- older age
- less-than-ideal body weight
- injecting street drugs
- hepatitis C virus co-infection
- prior diagnosis of osteonecrosis and fractures
- recent (in the past 12 months) diagnosis of cancer unrelated to AIDS
- recent (in the past 12 months) diagnosis of cardiovascular disease

People who entered the EuroSIDA study with relatively high CD4+ cell counts and people of colour had a significantly reduced risk for developing osteoporosis-related fractures.

## Risk factors for osteonecrosis

Among the 89 new instances of osteonecrosis, some of the risk factors that researchers found were as follows:

- prior diagnosis of osteonecrosis
- prior fractures
- prior AIDS
- prior AIDS-related cancer

As with the previous analysis of fractures, the EuroSIDA researchers found that people of colour had a reduced risk for osteonecrosis.

## The possible role of tenofovir

The current and widely used formulation of tenofovir (tenofovir disoproxil fumarate, TDF) which is in Truvada and several other medicines has been associated with an increased risk for bone problems.

A new formulation of tenofovir called TAF (tenofovir alafenamide) is gradually being introduced in high-income countries. It appears to be safer for bones (and kidneys).

In the EuroSIDA study, if participants used tenofovir, it would have been the older formulation.

Overall, researchers found that people who had been exposed to tenofovir had an increased risk for bone fractures. This risk was elevated in the

first year of use. If people continued to use the drug, the risk of developing a fracture remained elevated but stable; that is, it did not significantly increase further.

## Bear in mind

There are many factors that reduce the density of bone (and/or increase the risk for bone-related problems), such as the following:

- tobacco smoking
- excessive intake of alcohol
- use of corticosteroids

These factors were not analysed in the present study, perhaps because researchers did not have sufficient information on them.

EuroSIDA is an observational study and so it cannot prove a link between “cause and effect.” That is, the study cannot prove that what it identified as a risk factor did indeed cause the problems it was assessing. However, other studies have found broadly similar findings to the EuroSIDA study and so the results from this study are likely correct.

The researchers presented their findings at the Conference on Retroviruses and Opportunistic Infections. They barely had 10 minutes to do so (this time limit is often standard at most high-level international scientific conferences) and did not explain the context of some of their findings. For instance, the link between osteonecrosis and the diagnosis of a life-threatening infection or cancer that is the hallmark of AIDS may have arisen because patients with these conditions sometimes experience intense inflammatory reactions that require potent doses of anti-inflammatory drugs, such as corticosteroids. These drugs have been previously linked to the development of thinning bones. It is also possible that if patients were sufficiently ill to develop AIDS, they may have had untreated HIV infection for a long time. During that time they could have had malabsorption, been underweight and experienced excessive activation and inflammation of their immune system. In theory, all of these factors could have affected their bone density over time.

The link between fractures and a recent diagnosis of cardiovascular disease is interesting and should be further explored in other analyses.

## REFERENCE:

Borges AH, Hoy J, Florence E, et al. Antiretrovirals, fractures, and osteonecrosis in a large European HIV cohort. *Conference on Retroviruses and Opportunistic Infections*, 22–25 February 2016, Boston, MA. Abstract 46.

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## D. Zoledronic acid maintains bone density in ART users

People with HIV infection are at risk for thinner-than-normal bones and fractures. This risk for decreased bone density can arise because of multiple factors, some of which may be related to the impact of HIV on the immune system. Other factors are personal and may be related to at least the following issues:

- excessive alcohol intake
- tobacco smoking
- injecting street drugs
- use of corticosteroids

Studies have found that bone density tends to decrease by an average of 1% to 4% in the first year after ART is initiated. Bone density then tends to stabilize. The reason for this decrease in bone density is not clear.

Researchers in Atlanta, Georgia, conducted a small but well-designed clinical trial to assess the impact of a single infusion of the drug zoledronic acid (also known as zoledronate and sold under several brand names including Aclasta, Reclast and Zometa) on bone density in people initiating ART. The researchers found that a single infusion of zoledronic acid prevented ART-induced bone loss for one year (the duration of the study).

### Study details

Researchers screened 343 potential volunteers before selecting 63 who were randomly assigned to receive one of the following interventions:

- ART + a single infusion of zoledronic acid – 34 people
- ART + a single infusion of placebo (fake zoledronic acid) – 29 people

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

- age – 39 years
- 79% men, 21% women
- most (80%) participants were black
- at least 70% of participants were smokers (a risk factor for osteoporosis)

Researchers did not recruit pregnant women or anyone with bone disease, vitamin D deficiency or stomach ulcers.

All participants received the following once-daily ART: atazanavir (Reyataz) + Truvada (tenofovir + FTC).

### A note on assessment of bone health

Technicians analysed blood samples from participants for many proteins, but in particular for the following two proteins (or markers), which they used in part to assess bone health:

- CTx – c-terminal telopeptide of collagen. Elevated levels of this substance suggest that bones are being torn down (the technical term for this is resorption)
- osteocalcin – elevated levels of this protein suggest that bones are being built up

These blood tests are mainly used in research studies.

Technicians in the study also assessed bone health by having participants undergo low-dose X-ray scans called DEXA (dual-energy X-ray absorptiometry). Such scans are routinely used in clinics.

The study is expected to last 144 weeks and we now present preliminary findings.

### Results

Compared to placebo, levels of CTx fell significantly in zoledronic acid users by the following amounts at the following times:

- 73% decrease at week 12
- 65% decrease at week 24

Although the degree of decline in CTx was not as large at 48 weeks, it was still significantly greater than what was seen in people who received placebo.

Overall, this finding suggests that bone density was likely increasing in zoledronic acid users and decreasing in placebo users.

According to the results of DEXA scans of people who used zoledronic acid, bone mineral density rose by 8% in the spine at week 12, increased to 11% at week 24 and remained relatively stable by week 48. Similar trends were seen with DEXA scans of the hips.

In contrast, among placebo users bone mineral density fell by 2% at week 12, by 4% at week 24 and decreased slightly more at week 48.

Although the study was small, because of the relatively large effects captured by assessments, some sub-analyses were possible. Researchers found that zoledronic acid's beneficial effects were not affected by the following factors:

- race
- age (comparing people under 40 with older people)
- viral load
- the presence of osteopenia at the start of the study
- gender

However, researchers did note that among placebo users men were more likely to have bone thinning than women. Among people who used zoledronic acid, men seemed to be less likely to lose bone to resorption.

No significant differences in side effects were reported between people who received zoledronic acid and those who received placebo. The researchers suggested that the drug was well tolerated.

Researchers elsewhere have tested zoledronic acid to stabilize bone density in HIV-positive people. You can find links to these other studies in the bone health resources section.

## REFERENCE:

Ofotokun I, Titanji K, Vunnavu A, et al. A single dose of zoledronic acid prevents antiretroviral-induced bone loss. *Conference on Retroviruses and Opportunistic Infections*, 22–25 February 2016, Boston, MA. Abstract 47.

## E. Bone health resources

Here are some useful resources on bone health from previous issues of *TreatmentUpdate*:

- Bone health resources – *TreatmentUpdate* 209
- A clinical trial of zoledronate for increasing bone density – *TreatmentUpdate* 209
- Long-term effect of zoledronate on bone health in HIV-positive men – *TreatmentUpdate* 189

## II ANTI-HIV AGENTS

### A. Long-acting therapies—safety and other issues to consider

Potent combination anti-HIV therapy (commonly called ART) can help control HIV disease and help some people have near-normal lifespans. However, current formulations of ART need to be taken every day, sometimes twice daily, for the rest of a person's life.

Long-acting formulations of ART are under development. Such formulations could be offered as part of pre-exposure prophylaxis (PrEP) programs to help reduce a person's risk for becoming HIV infected. They could also be an attractive option for some HIV-positive people who are considering treatment for the first time.

Long-acting regimens simplify dosing because they would need to be taken infrequently—perhaps every six to eight weeks. Those currently in development need to be injected into the buttocks.

According to psychologists in New York, long-acting formulations “might be a particularly good fit for patients with disclosure concerns, who would benefit from having a shot administered in the privacy of a doctor's office, without needing to store medication on their person or in their house.”

More than five years ago, the pharmaceutical company ViiV Healthcare began to develop the experimental integrase inhibitor cabotegravir. In collaboration with another drug company called Janssen, ViiV has also been developing a long-acting formulation of rilpivirine, which belongs to a class of drugs called non-nukes.

Long-acting anti-HIV drugs have been in development longer than their oral, immediate-release counterparts. Some of the reasons for the longer development of these drugs arise because these formulations are new and have not been previously been tested in people. Below are some issues that need to be considered and explored with these experimental formulations; there are likely more.

### Drug levels and safety issues

1. Long-acting formulations are slowly released from the buttocks into circulation. In order to be sure that the amount of these drugs in the blood is at least adequate to reduce production of HIV, it is very likely that patients will first have to take oral (immediate-release) formulations of these drugs. How long will this period of oral medication-taking last?

2. An advantage of first taking an oral formulation of a regimen for several months is that it may allow sufficient time for doctors and nurses to detect any bothersome side effects. Key questions still under investigation are: What dose of a long-acting medicine is needed and how often will it need to be injected?

3. Should someone taking a long-acting regimen decide to discontinue receiving this formulation, how long will the long-acting formulation remain in the body? For potential PrEP users, this is critical information to help reduce the risk for developing drug-resistant HIV should long-acting formulations be approved as PrEP.

4. Another potential safety concern is drug interactions. If a person taking a long-acting formulation also takes another medicine and there is a drug interaction affecting levels of either or both drugs, this could result in the following issues:

- increased levels of the long-acting formulation, leading to new or intensified side effects

- decreased levels of the long-acting formulation, leading to reduced effectiveness and rising HIV levels
- higher-than-expected levels of the other medication, resulting in side effects
- reduced levels of the other medication, resulting in reduced effectiveness

In the case of people taking immediate-release regimens, it is relatively easy to deal with some drug interactions—they simply stop taking the offending medicine(s) and drug levels quickly fall. However, in the case of people taking long-acting formulations with infrequent dosing schedules, since the drug(s) is being constantly released into their system, there is no way to suddenly stop taking them.

Some conditions/treatments where drug interactions with long-acting formulations are possible may include the following:

- therapies for hepatitis C virus infection
- hormonal contraceptives
- antidepressants
- antipsychotics
- treatments for addictions

5. What do doctors do if a woman taking a long-acting formulation becomes pregnant? How do these drugs affect the growth and development of the fetus?

6. For now, long-acting therapies that are being developed as potential treatments are being tested only in people who have never previously used HIV treatment. So additional clinical trials will be necessary if treatment-experienced people wish to use these formulations.

### Other issues

Health policy planners are only just beginning to identify issues that might occur once long-acting formulations are licensed by regulatory authorities. At a minimum, basic themes that need to be explored and understood once licensure has occurred include distribution, storage and training of staff to perform intramuscular injections and maintain good clinical record keeping so that patients are recalled for injections in a timely manner. If all goes well in phase III trials, long-

acting formulations are not likely to be approved in Canada until at least 2019. As regulatory approval is relatively distant, it is premature to go into much detail about issues of how these drugs will be distributed and additional steps that may be likely to facilitate their use. However, it is noteworthy that long-acting cabotegravir does not require refrigeration but long-acting rilpivirine does. This may affect the deployment of the choice of these drugs for PrEP.

## REFERENCES:

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2. Andrews CD, Heneine W. Cabotegravir long-acting for HIV-1 prevention. *Current Opinion in HIV/AIDS*. 2015 Jul;10(4):258-63.
3. Arya V, Au S, Belew Y, Miele P, et al. Regulatory challenges in developing long-acting antiretrovirals for treatment and prevention of HIV infection. *Current Opinion in HIV/AIDS*. 2015 Jul;10(4):278-81.
4. Havlir D, Gandhi M. Implementation challenges for long-acting antivirals as treatment. *Current Opinion in HIV/AIDS*. 2015 Jul;10(4):282-9.
5. Meyers K, Golub SA. Planning ahead for implementation of long-acting HIV prevention: challenges and opportunities. *Current Opinion in HIV/AIDS*. 2015 Jul;10(4):290-5.
6. Margolis DA, Boffito M. Long-acting antiviral agents for HIV treatment. *Current Opinion in HIV/AIDS*. 2015 Jul;10(4):246-52.
7. Reese MJ, Bowers GD, Humphreys JE, et al. Drug interaction profile of the HIV integrase inhibitor cabotegravir: assessment from in vitro studies and a clinical investigation with midazolam. *Xenobiotica*. 2016 May;46(5):445-56.

## B. Long-acting cabotegravir—focus on safety

Cabotegravir is an experimental integrase inhibitor that is being tested in both immediate-release and long-acting formulation. In a study code named Éclair, researchers tested long-acting cabotegravir given by injection every 12 weeks to HIV-negative men who were at low risk for HIV infection. The purpose of Éclair was to assess the safety of the drug and to measure changes in the concentration of cabotegravir in the blood over time. Overall, the drug did not cause serious long-term side effects, though like all long-acting therapies there were temporary side effects related to pain at the site

of injection. Participants expressed satisfaction with long-acting therapy and said that they would prefer to receive it rather than oral immediate-release therapy. The best frequency of dosing for cabotegravir, were it to be used as part of a package of HIV prevention efforts, is not yet clear.

## Study details

Éclair had two parts as follows:

### Part 1 – Oral

In this oral lead-in phase, either cabotegravir (30 mg once daily) or placebo was taken for four consecutive weeks.

### Part 2 – Injection

Immediately following the oral phase, long-acting (LA) cabotegravir (800 mg) or placebo was administered by injection into muscle in the buttocks by study nurses. Specifically, a 2-mL solution of LA cabotegravir was injected into each buttock every 12 weeks over a period of 36 weeks. After the third injection, participants were monitored for an additional 40 weeks. One week after receiving each series of injections, participants returned to the study clinic for blood tests and other assessments.

The average profile of participants upon entering Éclair was as follows:

- age – 31 years
- HIV-negative and healthy men
- major ethno-racial groups – a majority of participants were white, the next largest group was black, followed by Latino

Researchers screened 205 participants. Out of these they selected 127 who were randomly assigned in a five-to-one ratio to the following interventions:

- cabotegravir – 105 men
- placebo – 21 men

## Results – Side effects in the oral phase

Most reported side effects were of mild-to-moderate intensity; however, 19% of participants on placebo and 23% on oral cabotegravir developed side effects that were of moderate-to-serious intensity. In general, the latter side effects were usually only

detected with laboratory testing of blood, such as the following:

- Elevated levels of the enzyme creatine phosphokinase. This has been reported as a rare side effect from integrase inhibitors; it may be associated with muscle weakness.
- Lower-than-normal levels of a group of white blood cells called neutrophils. However, this finding was not associated with any infection(s).
- A moderate degree of tiredness and unexpected lack of energy.

### Results – Side effects in the injection phase

Overall, 90% of participants on placebo developed a side effect, as did 98% of participants on cabotegravir.

The proportions of participants who experienced side effects of moderate, severe or serious intensity were as follows:

- placebo – 48%
- cabotegravir – 80%

These side effects were distributed as follows:

Pain at the injection site

- placebo – 5%
- cabotegravir – 59%

Fever

- placebo – 0%
- cabotegravir – 7%

Itchy skin at the injection site

- placebo – 0%
- cabotegravir – 6%

Swelling at the injection site

- placebo – 0%
- cabotegravir – 6%

One person who received placebo left the study because he developed a blood clot in his veins. One person taking cabotegravir developed an inflamed appendix.

### Focus on pain at the site of injection

In total, 27% of placebo and 92% of cabotegravir injections were associated with pain. The distribution of participants with different intensities of injection-site-related pain were as follows:

Mild pain

- placebo – 26%
- cabotegravir – 45%

Moderate pain

- placebo – 2%
- cabotegravir – 37%

Severe pain

- placebo – 0%
- cabotegravir – 10%

On average, among people who received injections of placebo, pain lasted for two days. Among people who received cabotegravir injections, pain lasted for over five days.

### At the injection site

The part of the body that receives an injection can have a temporary reaction to the substance injected. Such reactions include swelling that is soft, the formation of a small hard swelling called a nodule or bump, or bruising. Here is the distribution of some of these side effects:

Nodule/bump

- placebo – 0%
- cabotegravir – 8%

Bruising

- placebo – 2%
- cabotegravir – 6%

Most of these side effects resolved after a few days. However, people who received injections of cabotegravir and who developed a nodule/bump had them for an average of 10 days.

### Concentrations of cabotegravir

Injections of LA cabotegravir led to high concentrations of the drug in the blood of participants. After an injection, the levels of this drug would rise swiftly, reaching high levels within just one day. In theory, if LA cabotegravir was used

as PrEP, such high levels should provide a great degree of protection from infection with HIV. This estimation is based on the results of experiments with monkeys and the hybrid immune deficiency virus SHIV (simian-human immunodeficiency virus). In people who received cabotegravir, these high protective levels of the drug persisted for about eight weeks, sometimes a bit longer. However, in the present study there were some people, between 15% and 31% of participants, whose levels of cabotegravir in the blood were not always at the highly protective level.

All of this means that when it comes to protecting people from HIV infection (if LA cabotegravir were to be used as PrEP), a more frequent dosing interval will be required—perhaps every eight weeks.

### HIV infections

The Éclair study was designed to assess the safety of cabotegravir as well as how much of the drug built up in the blood (and how long it took for the drug to leave people's bodies). It was not designed to assess protection from HIV.

Two cases of HIV infection occurred during the study as follows:

One participant who was on placebo during the injection phase became HIV positive. He was referred to an infectious disease specialist for care.

The second man tested negative for HIV and its genetic material on routine blood tests done at regular intervals as part of the study. His last negative test result occurred at week 41 and analysis of his blood sample from that time found very low levels of LA cabotegravir since his last injection would have been at week 21. He disclosed to researchers that he had “unprotected sex with a casual partner between [study clinic] visits at weeks 41 and 53.”

At week 53, blood tests revealed that he had elevated levels of liver enzymes, suggestive of injury to this organ. His HIV viral load was 3.8 million copies/mL. He was referred to an infectious disease specialist for care and received a regimen of darunavir (Prezista) + ritonavir (Norvir) + Truvada (tenofovir + FTC).

Antibodies to HIV were not detected until a subsequent clinic visit at week 65.

Analysis of the strain of HIV with which he was infected did not detect any mutations or changes to the virus that would have allowed it to resist integrase inhibitors, including cabotegravir, or any other anti-HIV drug.

### Satisfaction

Researchers interviewed a sub-set of participants and many (74%) told researchers that they would prefer to continue to receive injections of LA cabotegravir rather than oral formulations. This level of satisfaction puts into context reports of temporary pain that can arise from injections of LA cabotegravir. However, readers should bear in mind that there was likely a degree of unintended bias in these survey results. That is, participants who chose to enter this study very likely wanted to receive injections of LA medicines rather than take oral formulations. This may explain the very high levels of satisfaction expressed toward LA cabotegravir by participants.

Éclair illustrates the complexities of clinical trials of long-acting formulations of anti-HIV drugs. There are still at least several years of clinical trials ahead before researchers will know if LA cabotegravir can provide a high degree of protection from HIV or whether, when used in combination with LA rilpivirine, it can act as part of therapy for people with HIV. Our next report explores the preliminary testing of LA formulations for HIV treatment.

### REFERENCE:

Markowitz M, Frank I, Grant R, et al. Éclair: phase 2A safety and PK study of cabotegravir LA in HIV-uninfected men. *Conference on Retroviruses and Opportunistic Infections*, 22–25 February 2016, Boston, MA. Abstract 106.

### C. Long-acting cabotegravir + rilpivirine for induction then maintenance therapy

As mentioned earlier in this issue of *TreatmentUpdate*, a long-acting formulation of the experimental integrase inhibitor cabotegravir is under development for pre-exposure prophylaxis (PrEP).

When long-acting cabotegravir is used together with another long-acting anti-HIV drug—rilpivirine (a non-nuke)—it is possible that this combination

may be useful as a form of treatment. This works by first reducing and keeping a patient's viral load at the 50-copy/mL mark with a combination that includes oral formulations of cabotegravir and rilpivirine. Doctors can then consider switching the patient's treatment to a dual regimen of the long-acting (LA) agents alone. Note that long-acting agents must be injected deep into muscle (usually in the buttocks), where they are slowly released into circulation over a period of weeks.

In a study called Latte-2, researchers tested the safety and effectiveness of LA formulations of cabotegravir and rilpivirine. They found that the formulations work with high rates of virological success. The final regimen that will be chosen for phase III clinical trials—injections every four or eight weeks—is not yet clear.

### Study details

Latte-2 had two parts, as follows:

#### Part 1

Participants received oral immediate-release cabotegravir at a dose of 30 mg once daily together with two other oral immediate-release anti-HIV drugs, abacavir + 3TC (both drugs are sold in one pill called Kivexa or Epzicom), also once daily. This oral regimen was taken for 20 consecutive weeks. In the final four weeks of this phase of the study, researchers added oral immediate-release rilpivirine, 25 mg once daily, to the regimens of participants.

#### Part 2

Participants were randomly assigned to one of three regimens, two of which featured long-acting formulations administered by injection. This phase of the study lasted for up to 96 weeks. The three regimens are as follows:

- cabotegravir 400 mg + rilpivirine 600 mg, both drugs given by injection every four weeks – 115 people
- cabotegravir 600 mg + rilpivirine 900 mg, both drugs given by injection every eight weeks – 115 people
- continued oral drugs – 56 people

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

- age – 35 years
- 92% men, 8% women
- viral load – 25,000 copies/mL
- 18% of participants had a viral load of at least 100,000 copies/mL
- CD4+ cell count – 490 cells/mm<sup>3</sup>

### Results

During the initial phase of the study about 95% of participants had a viral load less than 50 copies/mL

At the 32nd week of long-acting therapy, the following proportions of participants had a viral load less than 50 copies/mL:

- long-acting therapy injected every four weeks – 94% had a viral load less than 50 copies/mL
- long-acting therapy injected every eight weeks – 95% had a viral load less than 50 copies/mL
- oral cabotegravir-based regimen – 91% had a viral load less than 50 copies per mL

### Discontinuations

Here is the distribution of the proportion of participants who left the study prematurely because of adverse events:

- long-acting therapy injected every four weeks – 3%
- long-acting therapy injected every eight weeks – 0%
- oral regimen – 2%

Adverse events responsible for these premature departures from the study were as follows:

- HCV infection
- rash
- depression
- psychosis

## Focus on side effects

Side effects not related to injection site reactions were not common and were distributed by regimen as follows:

### Fever

- long-acting therapy injected every four weeks – 4%
- long-acting therapy injected every eight weeks – 3%
- oral regimen – 0%

### Unexpected lack of energy

- long-acting therapy injected every four weeks – 3%
- long-acting therapy injected every eight weeks – 2%
- oral regimen – 2%

### Flu-like illness

- long-acting therapy injected every four weeks – 2%
- long-acting therapy injected every eight weeks – 3%
- oral regimen – 0%

## Focus on injection site reactions

Overall, the most common injection site reactions were pain (67%), swelling (7%) and nodules (6%).

Here is the distribution of the severity of injection site reactions:

### Mild injection site reactions

- long-acting therapy injected every four weeks – 83%
- long-acting therapy injected every eight weeks – 80%

### Moderate injection site reactions

- long-acting therapy injected every four weeks – 16%
- long-acting therapy injected every eight weeks – 18%

### Severe injection site reactions

- long-acting therapy injected every four weeks – less than 1%
- long-acting therapy injected every eight weeks – 1%

In most cases (90%) these reactions subsided or resolved in one week or less.

## Satisfaction

When asked about their preferences for type of therapy (immediate release or long acting), most participants (more than 96%) were highly satisfied with a long-acting regimen and 98% told researchers that they would like to continue on it.

## Drug levels

Analyses of blood samples showed that cabotegravir levels were elevated though not always as high as what was seen with the oral 30 mg/day dosing schedule.

Rilpivirine levels were lower than expected but gradually increased to what would have been seen if the drug had been taken orally.

Researchers are collecting further data and will later decide which dose of both long-acting medicines to use in phase III studies.

Bear in mind that much research lies ahead and even if all goes well in phase III trials, long-acting therapies are not likely to be approved in Canada for HIV treatment until at least 2019.

## REFERENCE:

Margolis DA, González-García J, Stellbrink H-J, et al. Cabotegravir + rilpivirine as long-acting maintenance therapy: LATTE-2 week 32 results. *Conference on Retroviruses and Opportunistic Infections*, 22–25 February 2016, Boston, MA. Abstract 31LB.

## D. An emerging long-acting nuke

Researchers with the pharmaceutical company Merck have developed a new nucleoside analogue (commonly called a nuke) code-named MK-8591. The chemical shorthand for this drug is EFdA.

This new nuke has potent anti-HIV activity in lab experiments with HIV and cells. It works in part by interfering with an enzyme called reverse transcriptase, which is needed by HIV to successfully infect cells.

Animal studies suggest that the drug persists inside them, so phase I human studies were done to explore and understand this possibility.

In the phase I study (in humans), different doses of MK-8591 were taken orally—10, 30 or 100 mg once weekly for three weeks. According to Merck scientists, the drug is reportedly “well tolerated.” It lowers HIV viral load by about 1.64 log.

Merck has created long-acting injectable formulations of this drug. Experiments on rats suggest that a single injection of these formulations could provide high levels of MK-8591 in the blood for up to six months. Merck plans to test these formulations in people, perhaps administered every six months. If developed, MK-8591 may have potential as another form of pre-exposure prophylaxis (PrEP) or as treatment (when combined with other long-acting agents).

REFERENCE:

Grobler J, Friedman E, Barrett SE, et al. Long-acting oral and parenteral dosing of MK-8591 for HIV treatment or prophylaxis. *Conference on Retroviruses and Opportunistic Infections*, 22–25 February 2016, Boston, MA. Abstract 98.

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### E. An experimental drug that can protect cells from HIV in three different ways

The pharmaceutical company ViiV Healthcare has bought an unusual compound nicknamed combinectin. This drug was developed by another company called Bristol-Myers Squibb (BMS) and was designed to interfere with HIV’s ability to enter cells in three different and complex ways. Most of these involve impairing HIV’s ability to interact with key molecules on the surface of cells of the immune system. Combinectin (code named BMS-986197) has a protein molecule attached that helps it to resist being broken down.

Animal experiments suggest that combinectin has similar potency to standard triple anti-HIV therapy.

Researchers expect that combinectin may need to be injected once weekly, just under the skin, in monkeys and humans.

As ViiV has only recently bought this compound (along with a suite of different experimental anti-

HIV drugs from BMS), it may take several months for the corporation to prioritize the research and development plans for this and other drugs. Until those plans are completed, we will not know the development timeline for this unique drug.

REFERENCE:

Krystal M, Wensel D, Sun Y, et al. HIV-1 combinectin BMS-986197: a long-acting inhibitor with multiple modes of action. *Conference on Retroviruses and Opportunistic Infections*, 22–25 February 2016, Boston, MA. Abstract 97.

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### F. TAF + FTC—virus risk reduced in monkeys, but what about people?

The current formulation of tenofovir (sold as Viread) is often an important part of combination HIV prevention and treatment. Tenofovir is also found in several fixed-dose combinations such as the following:

- Truvada – tenofovir + FTC
- Stribild – elvitegravir + cobicistat + tenofovir + FTC
- Complera – rilpivirine + tenofovir + FTC

Tenofovir-containing medicines can cause side effects, particularly in some HIV-positive people who use it. These tenofovir-related side effects can include the development of thinning bones, a possible increased risk for fractures (as reported earlier in this issue of *TreatmentUpdate*), and kidney dysfunction. The original formulation of tenofovir is called TDF (tenofovir disoproxil fumarate).

A new formulation of tenofovir has been developed and is called TAF (tenofovir alafenamide). The pharmaceutical company that developed TDF is gradually releasing fixed-dose combinations containing TAF. The first TAF-containing combination that was approved in Canada and other high-income countries was Genvoya, which is similar to Stribild except instead of TDF it contains TAF. In clinical trials, TAF appears to be much safer than TDF.

### What about PrEP?

Truvada has been approved in Canada, the U.S. and some other countries for reducing the risk of HIV infection as part of a package of prevention measures. A major question is: Will the new version

of Truvada, which will contain TAF + FTC, be as effective in reducing the risk of HIV infection?

Unlike TDF, TAF does not accumulate in the blood but is taken up by cells of the immune system. These cells are targets for HIV, so, in theory, if these cells contain TAF (and FTC) they may be protected from HIV infection.

TDF was first tested in monkeys in the mid-1990s and was found to reduce their risk for becoming infected with SIV (simian immunodeficiency virus), which can cause an AIDS-like disease in susceptible monkeys. Experiments with monkeys were used to successfully guide the development of Truvada as PrEP. Now these same experiments with monkeys are being replicated with TAF + FTC.

The U.S. Centers for Disease Control and Prevention (CDC) has released data from experiments with monkeys exposed to low concentrations of the hybrid immune deficiency virus SHIV in the rectum. In these experiments, the monkeys were given either the combination of TAF + FTC (six animals) or placebo (six animals). These interventions (drugs and placebo) were given orally, 24 hours prior to being exposed to SHIV. Two hours after the monkeys were exposed to this virus, they were given another dose of TAF + FTC or placebo.

This schedule of dosing and virus exposure was done once weekly for a total of 19 weeks. However, after the first five weeks (and five exposures to the virus), the researchers put the trial on hold because they found that the animals that were given placebo were not becoming infected at the rate they expected (only two animals on placebo became infected). So the researchers rested the animals for a further five weeks during which time they did not receive drugs, placebo and virus. After this period the trial resumed and the animals received 14 more exposures to SHIV over 14 weeks.

Throughout the study the animals underwent weekly testing of their blood samples to check for possible infection. These tests included detection of any antibodies to the virus as well as tests that sought to find genetic material from SHIV. In addition, technicians assessed cells of the immune system from the animals for the concentration of TAF and FTC.

## Key results

Over the course of the study, all the placebo-treated animals became infected, while none of the animals treated with TAF + FTC became infected.

## Caution needed

In presenting this research at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI), the CDC researcher made the following statement:

“...while these data show that [TAF + FTC] protects [monkeys] against rectal SHIV infections, it should not be used in humans as a PrEP agent until clinical studies are complete and it is approved [by regulatory agencies] for PrEP”

Other experiments with women have found that TAF compared to TDF (both drugs given orally) results in about two to 10-fold lower concentrations of tenofovir in the vaginal and rectal tissues over 48 hours. What this will mean for protection from HIV is not clear. That is why it is important to wait for the results from a proposed clinical trial of TAF + FTC as PrEP.

Gilead Sciences is in discussion with the U.S. drug regulatory agency the Food and Drug Administration (FDA) about the clinical trial design(s) necessary to show that TAF + FTC can provide protection from HIV infection in people.

## REFERENCES:

1. Tsai CC, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl) adenine. *Science*. 1995 Nov 17;270(5239):1197-9.
2. Massud I, Mitchell J, Babusis D, et al. Chemoprophylaxis with oral FTC/TAF protects macaques from rectal SHIV infection. *Conference on Retroviruses and Opportunistic Infections*, 22–25 February 2016, Boston, MA. Abstract 107.
3. Garrett KL, Cottrell ML, Prince HA, et al. Concentrations of TFV and TFVdp in female mucosal tissues after a single dose of TAF. *Conference on Retroviruses and Opportunistic Infections*, 22–25 February 2016, Boston, MA. Abstract 102 LB.

### 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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