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I ANTI-HIV AGENTS

A. New drugs, new hope and possible timelines

At the recent Conference on Retroviruses and Opportunistic Infections (CROI), which took place in Seattle from February 13 to 16, 2017, researchers presented data about new anti-HIV compounds in development, including the following:

- a new integrase inhibitor – bictegravir
- a new nuke (NRTI) – code-named GS-9131
- a non-nuke (NNRTI) – doravirine
- a new protease inhibitor – code-named GS-PI1
- a capsid inhibitor (a new class of drug) – code-named GS-CA1

As all of these drugs are in development, they do not yet have brand names and in some cases they have only code names.

That these drugs are coming is good news for people who have HIV that is resistant to some medications. However, as these are all new drugs in development, they will take some time to come through the pipeline.

Timelines

The drugs that are closest to completing their final stages of clinical development are bictegravir and doravirine.

Bictegravir
Results from the main phase III studies of the integrase inhibitor bictegravir should become

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available in the latter half of 2017. The drug's manufacturer, Gilead Sciences, will then submit a dossier about bictegravir to regulatory authorities in Canada, the European Union and the U.S. and then to other countries. It will probably take a year before regulatory agencies finish reviewing the data, which means that bictegravir is unlikely to be approved until late summer or autumn of 2018. Once approved by Health Canada, bictegravir will have to undergo other secondary reviews and then Gilead will enter into negotiations with the provinces and territories about the drug's price and its place on their formularies (lists of subsidized medicines). Based on past trends, it is unlikely that bictegravir will be listed on formularies until sometime in the first half of 2019.

Doravirine

This non-nuke has completed most of the final phase of clinical trials. The doravirine dossier will hopefully be submitted by the pharmaceutical company Merck to regulatory authorities in Canada, the European Union and the U.S. later this year. Again, following past practices, it is likely that doravirine will not be approved until sometime in mid- to late 2018 and then it will probably take up to a year to be subsequently listed on provincial and territorial formularies. This means that doravirine is not likely to be on these formularies until mid- to late 2019.

The other drugs

All of the other drugs previously mentioned are made by Gilead Sciences and are in very early stages of development. Although their development details have not been released, the nuke GS-9131 is likely to enter phase I clinical trials in 2017. Phase I clinical trials assess the safety and preliminary effectiveness of a drug. If the drug proves safe and shows effectiveness, then it will move on to phase II. If all goes well, phase III trials could begin within two to three years.

The capsid inhibitor (GS-CA1) is the most interesting of the new compounds because it is the first drug of its kind to be developed. In experiments Gilead scientists noticed that the capsid inhibitor breaks down slowly. As a result, a long-acting formulation of the capsid inhibitor has been created. As no long-acting formulation of any anti-HIV drug has been approved, the development of the capsid inhibitor may take longer than if it were being developed as a standard formulation (immediate release). Gilead has to continue experiments with the capsid inhibitor in animals, and if those go well, phase I studies in people should hopefully begin in 2018.

The experimental protease inhibitor, code-named GS-PI1, appears to be furthest behind in the development timeline; clinical trials with this drug may not begin for several years.

In this issue of *TreatmentUpdate* we present information that was made available at CROI about these emerging therapies.

B. The capsid inhibitor—a new class to enter clinical trials

Most approved anti-HIV drugs work by interfering with an enzyme and/or protein that is needed by HIV-infected cells to make new viruses.

A journey through the cell

The capsid is the name given to the proteins that surround HIV's genetic material. Upon HIV attaching itself to a target cell of the immune system, the virus sends its genetic material (RNA) into the cell. As the genetic material is surrounded by the capsid, it is protected from detection by the cell's internal sensors. The capsid, along with its cargo of genetic material, then makes its way to the cell's control centre, or nucleus. Inside the nucleus is the cell's genetic material, which contains instructions for the operation of the cell and helps it carry out its functions. Once near the nucleus, the capsid releases its cargo, and through a series of steps HIV's genetic material is converted into a form similar to the cell's genetic material (DNA). The capsid proteins then help HIV's DNA cross into the nucleus, where it integrates into the cell's DNA. At some point in the future, perhaps through immunological stimulation, the cell becomes activated and HIV's DNA takes over the cell and converts it into a mini-virus factory, producing new copies of HIV.

More about the capsid

The capsid has several functions, as follows:

- it protects HIV's genetic material
- it helps HIV's genetic material gain entry to the nucleus of a cell
- it helps the new copies of HIV become infectious

Thus, a capsid inhibitor could work by interrupting or impairing three different parts of HIV's life cycle. In theory, since the capsid inhibitor has so many anti-HIV activities, it could be used by itself in the prevention of HIV infection. However, much work lies ahead before this drug's developer, Gilead Sciences, can be certain about that. A long-acting formulation of the capsid inhibitor has been developed and can maintain high levels in dogs for at least 10 weeks. This finding suggests that the capsid inhibitor has potential for intermittent dosing in people—perhaps every one or two months. However, this formulation likely will need further testing in animals, particularly in monkeys susceptible to SIV (simian immunodeficiency virus, which is closely related to HIV), before human studies begin. Taking all of this information into account, clinical trials with the capsid inhibitor may not begin until 2018.

REFERENCE:

Tse WC, Link JO, Mulato A, et al. Discovery of novel potent HIV capsid inhibitors with long-acting potential. *Conference on Retroviruses and Opportunistic Infections*, 13-16 February 2017, Seattle. Abstract 33.

C. Bictegravir—an emerging integrase inhibitor

Bictegravir (formerly GS-9883) is a potent integrase inhibitor under development for the treatment of people with HIV. Bictegravir is made by Gilead Sciences.

In laboratory experiments with cells and HIV, bictegravir can work against many strains of HIV that are resistant to other integrase inhibitors, such as raltegravir (Isentress) and elvitegravir (in Genvoya and Stribild). Bictegravir is also effective against some strains of HIV that are resistant to another integrase inhibitor, dolutegravir (Tivicay and in Triumeq).

In a phase II randomized clinical trial, researchers gave 131 people who had not previously used HIV therapy bictegravir or dolutegravir, each drug taken with a backbone of TAF (tenofovir alafenamide) and FTC (emtricitabine). Both bictegravir- and dolutegravir-containing regimens performed well over 48 weeks, with more than 90% of participants achieving a viral load less than 50 copies/mL. Side effects were common but were mostly mild or moderate. No side effects were graded as serious and no one died in the study.

Bictegravir, which will be co-formulated (put into one pill) with TAF and FTC, can be taken once daily. Phase III clinical trials are underway with the bictegravir-containing combination and results should be available in the second half of 2017. A trial with about 470 HIV-positive women using a bictegravir-containing regimen is planned for later in 2017.

Study details

Researchers in the U.S. randomly assigned participants in a 2:1 ratio to receive the following:

- bictegravir (75 mg) + TAF + FTC – 65 participants
- dolutegravir + TAF + FTC – 33 participants

Participants could take the study medicines with or without food, once daily. Several doses of bictegravir have been assessed in earlier studies and as a result of these studies Gilead scientists have decided that the 75-mg daily dose is best.

The average profile of participants in the study was as follows:

- men – 96%, women – 4%
- age – 31 years
- 94% of participants were free from symptoms related to HIV disease
- viral load – 25,000 copies/mL
- CD4+ count – 444 cells/mm^3
- estimated glomerular filtration rate (eGFR; a measure of kidney health) – 125 mL/minute

The study lasted for 48 weeks.

Results—Changes in viral load

Regimens based on integrase inhibitors can quickly drive down viral load in the blood and the drugs used in this study were no exception.

Week 12
By the 12th week of the study, 94% of all participants had a viral load less than 50 copies/mL in their blood samples.

Week 24
By the 24th week of the study, small differences in the proportion of participants who were virologically suppressed emerged as follows:

- bictegravir-based regimen – 97% had a viral load less than 50 copies/mL
- dolutegravir-based regimen – 94% had a viral load less than 50 copies/mL

Week 48
By the 48th week of the study, the distribution of participants with suppressed viral loads was as follows:

- bictegravir-based regimen – 97% had a viral load less than 50 copies/mL
- dolutegravir-based regimen – 91% had a viral load less than 50 copies/mL

None of these differences in viral loads was statistically significant.

A closer look

Using a more sensitive viral load assay with a lower limit of 20 copies/mL, the distribution of suppressed viral loads at week 48 was as follows:

- bictegravir-based regimen – 91% had a viral load less than 20 copies/mL
- dolutegravir-based regimen – 88% had a viral load less than 20 copies/mL

This difference in viral loads was not statistically significant.

According to the study team, adherence among a minority of dolutegravir users was less than ideal. This may have affected the results.

Changes in CD4+ cell counts

On average, participants taking bictegravir had 258 more CD4+ cells by the end of the study and dolutegravir users had 192 more CD4+ cells. This difference was not statistically significant.

Side effects

Overall, side effects were distributed as follows:

- bictegravir-based regimen – 85% developed side effects
- dolutegravir-based regimen – 65% developed side effects

The distribution of specific side effects was as follows:

Diarrhea
- bictegravir-based regimen – 12%
- dolutegravir-based regimen – 12%

Nausea
- bictegravir-based regimen – 8%
- dolutegravir-based regimen – 12%

Bone pain
- bictegravir-based regimen – 6%
- dolutegravir-based regimen – 6%

Fatigue
- bictegravir-based regimen – 6%
- dolutegravir-based regimen – 6%

Liver enzymes

In general, neither regimen was associated with any signals of toxicity to major organ-systems. However, temporarily elevated liver enzyme (ALT, AST) levels in the blood seemed more likely to occur among a minority of bictegravir users—between 6% (ALT) and 9% (AST). The reasons for this are not clear. In one case the researchers underscored that a participant had recently become infected with hepatitis C virus and also drank excessive amounts of alcohol. Both of these factors cause liver injury and inflammation and would increase liver enzyme levels in the blood. As for all the other participants with temporarily elevated liver enzymes, as this was a relatively small study, some of those findings could have occurred by chance.

Creatine kinase

Elevated levels of the enzyme creatine kinase (also called creatine phosphokinase) were found in the blood of 13% of participants who were taking bictegravir and 9% of those taking dolutegravir. These elevations were temporary.

Elevated levels of these enzymes can occur in cases of muscle inflammation and injury. For example, if a blood sample was drawn after lifting weights or engaging in resistance exercises, levels of creatine kinase would be temporarily elevated. Other researchers have documented persistently elevated creatine kinase levels in a very small proportion of patients who were experiencing muscle injury arising as a side effect of the integrase inhibitor raltegravir (Isentress). However, in the present clinical trial, researchers did not think that the temporarily increased levels of creatine kinase were a consequence of drug side effects from bictegravir or dolutegravir, which have chemical structures somewhat similar to raltegravir.

Bear in mind

This is a small phase II clinical trial. As a result, firm conclusions about which regimen is better cannot be drawn. Phase II studies are designed to find preliminary evidence of safety and effectiveness that can then be explored in a trial of a more robust statistical design, such as a randomized phase III study. Phase III clinical trials are underway to assess bictegravir's potential against dolutegravir and other anti-HIV drugs. The results from these studies should become available in the latter half of 2017. Bictegravir is also being tested in treatment-experienced patients and a trial to better assess bictegravir's safety in women is being considered by Gilead.

REFERENCES:

1. Sax PE, DeJesus E, Crofoot G, et al. Randomized trial of bictegravir or dolutegravir with FTC/TAF for initial HIV therapy. *Conference on Retroviruses and Opportunistic Infections*. 13-16 February 2017, Seattle. Abstract 41.

2. Lee FJ, Amin J, Bloch M et al. Skeletal muscle toxicity associated with raltegravir-based combination antiretroviral therapy in HIV-infected adults. *Journal of Acquired Immune Deficiency Syndromes*. 2013 Apr 15;62(5):525-33.

3. Calza L, Danese I, Colangeli V, et al. Skeletal muscle toxicity in HIV-1-infected patients treated with a raltegravir-containing antiretroviral therapy: a cohort study. *AIDS Research and Human Retroviruses*. 2014 Dec;30(12):1162-9.

D. Bictegravir in the body—preliminary information about drug interactions

Bictegravir (formerly GS-9883) is an experimental integrase inhibitor being developed by Gilead Sciences and is currently in phase III clinical trials. Below is some preliminary information about the drug.

It is powerful and active against many strains of HIV that are resistant to the following integrase inhibitors:

- elvitegravir (in Genvoya and Stribild)
- raltegravir (Isentress)

Bictegravir is also effective against some strains of HIV that are resistant to the integrase inhibitor dolutegravir (Tivicay and in Triumeq).

A single 75-mg dose of bictegravir is sufficient to maintain levels of this drug in the blood so that once-daily dosing is sufficient.

Bictegravir is well absorbed and is slowly broken down by these enzymes in the body—CYP3A4 and UGT1A1.

After bictegravir is licensed, the manufacturer will release instructions about how it should be used, along with information about potential and actual drug interactions. In the meantime, here is some preliminary information about some drug interactions with bictegravir.

Acid-reducing agents, laxatives, metal supplements and buffered medicines

Gilead Sciences recommends that bictegravir be taken 2 hours before or 2 hours after taking the following medicines.

Acid-reducing agents, including the following:

- Alka-Seltzer
- Gaviscon (tablets and syrup)
- Maalox (liquid and tablets)
- Milk of Magnesia
- Pepto-Bismol and Pepto Bismol Childen's
- Rolaids
- Tums

Metal supplements including those containing iron, calcium and magnesium should also follow the same two hour guidance.

Antibiotics
Drugs such as rifabutin and rifampin speed up the activity of the enzymes CYP3A4 and UGT1A1. Taking these drugs can reduce the amount of bictegravir in the blood between 38% (in the case of rifabutin) and 75% (in the case of rifampin).

Antifungal drugs
The drug voriconazole (Vfend) impairs the activity of the enzyme CYP3A4 and raises bictegravir concentrations by 61%.

Diabetes drugs
Metformin (Glucophage) is commonly prescribed by doctors as part of a plan to help control blood sugar. Bictegravir can increase levels of metformin in the blood by almost 40%. This could lead to side effects such as nausea and diarrhea in some people who use metformin. It is likely that doctors may have to reduce the dose of metformin in bictegravir users. A similar issue occurs with the use of another integrase inhibitor, dolutegravir, and metformin.

Hepatitis C drugs
Bictegravir does not affect the concentrations of the drugs (ledipasvir and sofosbuvir) that are co-formulated and sold as Harvoni. Gilead has not released information about potential interactions between bictegravir and hepatitis C medicines made by other companies.

HIV protease inhibitors
The drug atazanavir (Reyataz) inhibits the activity of CYP3A4 and UGT1A1 and can therefore significantly raise bictegravir levels by 310%.

Hormones
Bictegravir does not affect levels of commonly used forms of estrogen (norgestimate and ethinyl estradiol) that are in contraceptive pills.

A treatment in one pill

Bictegravir will be co-formulated with the following two other drugs:

- TAF (tenofovir alafenamide; the new, safer version of tenofovir)
- FTC (emtricitabine)

All three drugs in one pill will provide a complete treatment option.

Tests have shown that all three drugs are well absorbed when taken together. When all three drugs are taken with food, the absorption of bictegravir increases by about 24%. This is not seen as clinically significant and so the company recommends that all three drugs can be taken with or without food.

REFERENCE:

Zhang H, Custudio JM, Wei X, et al. Clinical pharmacology of the unboosted integrase strand transfer inhibitor bictegravir. Randomized trial of bictegravir or dolutegravir with FTC/TAF for initial HIV therapy. *Conference on Retroviruses and Opportunistic Infections*. 13-16 February 2017, Seattle. Abstract 40.

E. A new nuke in the works—GS-9131

Gilead Sciences is developing a new nucleoside analogue (nuke) code-named GS-9131. Once inside of cells, GS-9131 becomes activated by enzymes and turns into a compound with anti-HIV activity called GS-9148. Drugs that are taken in one form and then converted into another form once in the body are called pro-drugs. So far research suggests that GS-9131 (or GS-9148) is not likely to accumulate in kidney cells or harm the parts of the cell that generate power (mitochondria). This is important because older nukes tended to injure mitochondria and cause problems for users. Also, an earlier version of the nuke tenofovir DF (tenofovir disoproxil fumarate) tended to accumulate in the kidneys of some patients and cause kidney dysfunction.

For the rest of this brief report we will refer only to GS-9131 for the sake of simplicity.

Activity against HIV

There are two main strains of HIV as follows:

- HIV-1 – the most common strain
- HIV-2 – a less common strain found mostly in parts of West Africa

HIV-1 can be further subdivided into many subtypes such as A, B, C, D and so on. Subtype B is most commonly found in North America, Central and South America, Western Europe, Japan, Australia

and New Zealand. In lab studies with cells and HIV, GS-9131 is active against many subtypes of HIV.

GS-9131 is also active against some strains of HIV that have arisen because of resistance to the following nukes:

- abacavir (Ziagen and in Kivexa and Trizivir)
- emtricitabine (FTC and in Truvada and many other combinations)
- ddI (Videx)
- AZT (Retrovir and in Combivir and Trizivir)
- d4T (Zerit)
- tenofovir DF (Viread and in Truvada and many other combinations)

GS-9131 has increased antiviral activity against HIV when it is combined with the following drugs:

- TAF (tenofovir alafenamide; the new, safer formulation of tenofovir)
- tenofovir DF
- abacavir
- efavirenz (Sustiva, Stocrin and in Atripla)
- nevirapine
- darunavir (Prezista and in Prezcobix)
- dolutegravir (Tivicay and in Triumeq)
- bictegravir

Thus, GS-9131 may be useful as part of regimens for people who have strains of drug-resistant HIV. Initial clinical trials of this drug should begin in 2017.

REFERENCE:

White K, Margot N, Stray K, et al. GS-9131 is a novel NRTI with activity against NRTI-resistant HIV-1. *Conference on Retroviruses and Opportunistic Infections*, 13-16 February 2017, Seattle. Abstract 436.

F. Doravirine vs. darunavir

Doravirine is an experimental non-nuke that is undergoing phase III clinical trials. It is designed to be effective against most strains of HIV that are resistant to other non-nukes, such as the following:

- efavirenz (Sustiva, Stocrin and in Atripla)
- nevirapine
- rilpivirine (Edurant and in Complera)

Doravirine can be dosed once daily with or without food. In addition to being developed in a 100-mg pill, doravirine is also being developed as a fixed-dose formulation with the following two drugs:

- tenofovir DF (Viread and in Truvada and many other combinations)
- 3TC (lamivudine and in Triumeq and many other combinations)

Merck, the developer of doravirine, recently conducted a randomized, placebo-controlled study comparing regimens based on doravirine to regimens based on darunavir (Prezista and Prezcobix). Darunavir is the leading protease inhibitor used in high-income countries today. It has to be taken with a small dose of another drug, ritonavir (Norvir), which helps to boost or maintain levels of darunavir in the blood so that it can be taken only once daily. In its clinical trial Merck found that doravirine was roughly equivalent in potency to darunavir-based regimens.

Study details

Upon entering the study the average profile of participants was as follows:

- no participants had previously used HIV drugs and no participants were infected with HIV that was resistant to doravirine or darunavir
- age – 35 years
- 84% men, 16% women
- 10% had symptoms of AIDS in the past
- 70% had the strain of HIV that is most common in North America and Western Europe – subtype B
- viral load – 25,000 copies/mL
- 20% of participants had a viral load greater than 100,000 copies/mL
- CD4+ count – 422 cells/mm^3
- 14% of participants had a CD4+ count of 200 cells/mm^3 or less

The nukes used in this study were as follows:

- tenofovir DF + FTC
- abacavir + 3TC

Data were released on study participants after one year. Their distribution was as follows:

- doravirine-based regimen – 327 people
- darunavir-based regimen – 312 people

The study will continue for two years.

Results—Changes in viral load and CD4+ cell counts

Overall, after one year, the proportions of participants who had a viral load less than 50 copies/mL were distributed as follows:

- doravirine-based regimens – 84%
- darunavir-based regimens – 80%

Statistical analysis found that both regimens are roughly equivalent (the technical term for this is non-inferior).

The following proportions of participants were unable to keep their viral load suppressed:

- doravirine-based regimens – 11%
- darunavir-based regimens – 13%

Data from the remaining participants was not yet available.

Among participants who entered the study with a viral load greater than 100,000 copies/mL, the proportions with a suppressed viral load at week 48 were as follows:

- doravirine-based regimens – 81%
- darunavir-based regimens – 76%

Among participants who entered the study with a CD4+ count greater than 200 cells/mm^3, the proportions that were virologically suppressed at week 48 were as follows:

- doravirine-based regimens – 89%
- darunavir-based regimens – 89%

Among participants who entered the study with a CD4+ count between 51 and 200 cells/mm^3, the proportions with a suppressed viral load at week 48 were as follows:

- doravirine-based regimens – 83%
- darunavir-based regimens – 74%

Among participants who entered the study with a CD4+ count of 50 or less cells/mm^3, the proportions with a suppressed viral load at week 48 were as follows:

- doravirine-based regimens – 83%
- darunavir-based regimens – 67%

CD4+ cell counts increased over the course of the study. Below are the average increases in e cell counts for each regimen by week 48:

- doravirine-based regimens – 193 cells/mm^3
- darunavir-based regimens – 186 cells/mm^3

This difference in CD4+ cell counts was not statistically significant.

Side effects

About 30% of all participants experienced side effects; this is relatively common when people begin HIV treatment in or out of clinical trials. In most cases, side effects should fade after a few weeks. However, 2% of participants on doravirine and 3% on darunavir had to quit the study due to side effects.

Common side effects were distributed as follows:

Diarrhea
- doravirine-based regimens – 14%
- darunavir-based regimens – 22%

Nausea
- doravirine-based regimens – 11%
- darunavir-based regimens – 12%

Headache
- doravirine-based regimens – 11%
- darunavir-based regimens – 14%

Rash
- doravirine-based regimens – 7%
- darunavir-based regimens – 8%

Focus on the brain

All non-nukes are based on a chemical structure distantly related to Valium-type drugs. This means that they can get inside the brain, which is a sanctuary for HIV. However, it also means non-nukes have the potential to cause brain-related side

effects (also called neuropsychiatric side effects). As an example, efavirenz was a first-generation non-nuke that is notorious for causing brain-related side effects. Examples of brain-related side effects include the following:

- concentration problems
- confusion
- dizziness
- difficulty falling asleep and/or staying asleep
- vivid dreams
- in rare cases depressive illness

We do not have detailed information about brain-related side effects from this study.

The overall distribution of brain-related side effects was as follows:

- doravirine-based regimens – 11%
- darunavir-based regimens – 13%

No participant left the study because of these side effects.

Abnormal lab test results

Analysis of blood samples from participants detected few severe abnormalities. If abnormal test results did occur, for the most part they were generally of mild to moderate intensity.

Here is the distribution of severely abnormal elevated blood test results:

LDL-C ("bad cholesterol")
- doravirine-based regimens – less than 1%
- darunavir-based regimens – 3%

Blood sugar
- doravirine-based regimens – 1%
- darunavir-based regimens – less than 1%

AST (a liver enzyme)
- doravirine-based regimens – 1%
- darunavir-based regimens – 3%

ALT (a liver enzyme)
- doravirine-based regimens – 1%
- darunavir-based regimens – 2%

Creatinine (used to assess kidney health)
- doravirine-based regimens – 1%
- darunavir-based regimens – 3%

Creatine kinase (sometimes called creatinine phosphokinase)
Elevated levels of creatine kinase indicate that muscle inflammation and injury may be occurring. However, given the low levels of this issue found in this study (regardless of the regimen used) and that there were no complaints about muscle pain, it is unlikely that this was a problem.

- doravirine-based regimens – 2%
- darunavir-based regimens – 2%

More about cholesterol and triglycerides

Over the long-term, elevated levels of LDL-C are associated with an increased risk for cardiovascular disease. In the present study, when analyses were done on blood samples for their lipid (cholesterol and triglyceride) levels, researchers asked participants to fast before the samples were collected. As a result of deeper analysis of lipid levels, researchers found that there was a small but significant increase in LDL-C levels among participants taking darunavir. In contrast LDL-C levels fell modestly in doravirine users. Triglycerides also rose among darunavir users but declined in doravirine users.

Levels of HDL-C ("good cholesterol") rose modestly in participants regardless of which study drug they used.

Summary

Overall, the study shows that doravirine is not inferior to darunavir and is a potent and highly effective treatment, particularly for people who are initiating HIV therapy, with only some participants experiencing side effects.

REFERENCE:

Molina J-M, Squires K, Sax P, et al. Doravirine is non-inferior to darunavir + ritonavir in a phase 3 treatment-naïve trial at week 48. *Conference on Retroviruses and Opportunistic Infections*. 13-16 February 2017, Seattle. Abstract 45 LB.

II MALE SEXUAL HEALTH

A. Some issues related to sexual dysfunction in men

Thanks to the power of modern HIV treatment (ART) many HIV-positive people in Canada and other high-income countries who are aware of their status and engaged in their care and treatment and who do not have serious co-infections, unmanaged mental health conditions or addiction, are expected by researchers to have a near-normal life expectancy. ART also has another great effect: By suppressing HIV to levels so low that they are undetectable with routine lab tests, and when people continue to take ART every day so that their viral load stays undetectable, studies have found that HIV-positive people do not pass on the virus to their sexual partners. Given these twin benefits of ART, a healthy sex life contributes to good quality of life and from time to time sexual dysfunction can be a problem for some men living with HIV. In general, there is less research on female sexual dysfunction and far less on such dysfunction in women with HIV.

In this issue of *TreatmentUpdate* we review key ideas about male sexual dysfunction.

Erectile dysfunction

The inability to get and maintain a firm erection is called erectile dysfunction (ED). This is one of the more common problems that all men can experience.

It is difficult to be certain how common ED is among HIV-positive men because many studies that have collected data about ED did not focus on this issue and explore it. Despite this shortcoming, studies suggest that between 50% and 60% of HIV-positive men who were surveyed disclosed that they have experienced ED. As ED can be a difficult subject to talk about, it is possible that more men have ED than have disclosed this problem in surveys.

There are many factors that can underpin ED—sometimes there may be biological reasons, other times there may be psychological reasons, and still other times there may be a combination of these two areas that underpin ED. Whatever the cause of ED in an individual, diagnosis should usually prompt a discussion between doctor and patient about it. This may lead to an investigation by the doctor and/or referral to a specialist such as a urologist, endocrinologist, psychologist, psychiatrist or others as needed.

Key risk factors for ED

ED occurs in HIV-negative men and the same risk factors that operate in that population may also affect HIV-positive men or may be accentuated in them. Below are some possible risk factors for ED.

Smoking
This is a well-established risk factor for ED.

Low testosterone levels
HIV infection can reduce levels of testosterone and other hormones. A key part of ruling out lower-than-normal levels of testosterone as a cause of ED is a blood test for this hormone.

Note that there are antibodies in the blood that bind to testosterone. Only the testosterone that is unbound is available for use by the body's cells. This unbound testosterone is called "free testosterone." Thus, when getting testosterone measured, specialists often request that free testosterone be assessed by laboratories.

Studies have found that HIV-positive men, whether or not they are using ART, tend to have lower-than-normal levels of testosterone (a condition called hypogonadism). This may be caused by HIV directly as HIV-infected cells produce compounds that may injure the testicles (a major source of testosterone), or it may be caused indirectly through the ongoing inflammation that is associated with HIV disease.

Abnormal lipid levels
Cholesterol and triglycerides are fatty substances (lipids) in the blood. Abnormal concentrations of these are associated with an increased risk for cardiovascular disease. Prolonged abnormal levels of lipids in association with ED suggests the possibility that problems with blood circulation are developing and possibly affecting the flow of blood to and retention of blood within the penis.

Type 2 diabetes
ED is common in males with type 2 diabetes likely because diabetes can affect circulation of blood and is associated with nerve injury.

Elevated blood pressure
It is normal to have higher-than-normal blood pressure while exercising or during stressful periods. However, prolonged higher-than-normal blood pressure can injure blood vessels and organs. Elevated blood pressure is a risk factor for ED.

Circulatory issues
Good flow of blood is necessary to achieve an erection. Not only must blood flow into the penis, it must stay there for the duration of sex. However, in cases where blood vessels are partially blocked due to cardiovascular disease, ED can occur. Injury to the penis from trauma can also affect the circulation of blood in that area.

Obesity
This is another well-established risk factor for ED.

Psoriasis
Emerging research suggests the possibility that some men who have psoriasis may be at increased risk for ED.

Psychological issues
Factors affecting mental health can affect sexual health and functioning. For instance, anxiety and depression can also contribute to ED.

Unfortunately, HIV is still a stigmatized condition and some HIV-positive men may worry about inadvertently passing on the virus to their sexual partners. This and other worries can contribute to ED. Also, doctors have generally found that even if ED was ultimately triggered by biological factors, the presence of ED can then incite the development of psychological issues that play a role in prolonging ED.

Some men may also experience feelings of no longer feeling sexually desirable.

In cases where there is a psychological component underpinning ED, referral to a therapist may be useful.

Medicines

Some classes of medicines may increase the risk of ED and some even cause problems with orgasm and/or ejaculation. The following classes of drugs have been associated with ED in some men. A review with your pharmacist can help you identify if the medicines that you are using are on this list of drug classes. Note that there might be drugs/classes that are not listed that may also be linked to ED and this is yet another reason why conversations with pharmacists (in addition to doctors) are important when investigating drug side effects.

- anabolic steroids
- anti-anxiety medicines
- some antidepressants
- some antacids called histamine-2 antagonists
- some antiseizure drugs
- drugs to reduce high blood pressure
- calcium channel blockers
- some diuretics (thiazides and spironolactone)
- hormones – estrogens and corticosteroids
- recreational drugs – alcohol, cocaine, marijuana, methamphetamine

ART

There is no firm evidence that ART causes ED. This issue is explored in the following report in this issue of *TreatmentUpdate*. However, Italian doctors who study HIV and ED have suggested that doctors treating HIV-positive patients consider the possibility of changing a person's HIV treatment if "ED appeared soon after starting [this treatment]."

Screening and treatment of ED

The Italian doctors also recommended that HIV-positive men receive counselling to help them reduce modifiable risk factors they may have that are contributing to ED. Such factors could include the following:

- cigarette smoking
- insufficient exercise
- obesity
- alcohol and/or other substance use

A next step is to include assessments to uncover underlying biological and hormonal risk factors (including diabetes, reduced testosterone levels, abnormal lipid levels in the blood, and so on). If such problems are found, treating them can help improve overall health and quality of life and perhaps ED.

The most common drugs to treat ED are inhibitors of an enzyme called PDE-5 and include the following:

- Cialis
- Levitra
- Viagra

One of these will usually work for ED. However, in cases where these drugs do not work, referral to a urologist for further investigation can be a useful next step. Note that these drugs can interact with some medicines and recreational substances, so a discussion with your doctor and pharmacist about possible interactions and side effects of ED treatment is necessary.

A note about diet

Observational studies suggest that diet can play a role in reducing the risk of developing ED in HIV-negative men. A longitudinal U.S. study that collected data between the years 2000 and 2008 on more than 25,000 men found that those who ate diets high in certain fruits (including strawberries, blueberries, apples, pears and citrus) had a 14% reduced risk for developing ED compared to men who did not eat such a diet. These fruits contain naturally occurring compounds that act as antioxidants and can help to reduce inflammation. When researchers focused on fruits with the highest amount of these compounds—citrus and blueberries—the risk of developing ED was reduced by 19%. These effects were most likely in men who were less than 70 years old. These findings should not be misinterpreted to mean that citrus and blueberries can stop ED or are of equivalent potency to ED treatments. Instead, these colourful fruits seem to help reduce the *risk* for developing ED. They are not a substitute for engaging in other aspects of healthy living (such as quitting smoking, losing weight, engaging in daily exercise and so on).

A much smaller observational study in 65 men, half of whom ate a Mediterranean-type diet (rich in whole grains, fruit, vegetables, nuts, legumes and olive oil) found that those on the diet were less likely to develop ED. Such diets have been known to reduce the risk of type 2 diabetes and cardiovascular disease; that they might have related benefits (such as on ED) is not surprising.

Since diets high in colourful fruits and vegetables have generally beneficial effects, they should also improve the overall health of HIV-positive people and may have an impact on reducing the risk of ED in some HIV-positive men.

Sexual dysfunction

In addition to ED there are other forms of sexual dysfunction that can occur in men, such as reduced sexual desire or interest in sex. These problems can occur because of anxiety, depression, relationship difficulties and other issues. Loss of interest in sex can occur because of reduced testosterone levels. Some people, for many reasons, may no longer feel desirable.

Thus, in some cases, much investigation by family doctors and/or other specialists may be required to unravel and understand possible factors underlying sexual dysfunction and how to deal with them. This requires time and patience.

More research is needed to understand sexual dysfunction in HIV-positive men and ways to remedy this issue.

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B. Do integrase inhibitors affect testosterone levels in men?

Lower-than-normal levels of testosterone in men are associated with the following problems:

- decreased interest in sex
- erectile dysfunction
- reduced muscle mass and strength
- thinning bones
- fatigue
- in some cases, depression

Decreased testosterone levels occur as all men age.

In the time *before* potent HIV treatment (ART) became available, researchers found low testosterone levels in some men with HIV. In such cases this problem may have arisen for several reasons, including the following:

- unintentional and severe weight loss (due to HIV disease)
- HIV-related inflammation and injury to the body's hormonal networks
- the development of life-threatening infections and prolonged and intense regimens of antibiotics, antifungals and antivirals needed to treat and later prevent infections from recurring

However, lower-than-normal levels of testosterone also have been found among HIV-positive men in the subsequent era who were using ART and never developed AIDS.

The reasons for this are not clear but may be related to dysfunction in the body's production of some hormones, including testosterone, perhaps arising directly or indirectly from HIV infection.

Decreased testosterone levels have also been linked to the following:

- excessive intake of alcohol
- injecting street drugs
- hepatitis C virus infection

Measuring testosterone

There are antibodies in the blood that bind to hormones such as testosterone. The unbound (or "free") testosterone is what is available for use by the body's cells. Therefore, when assessing testosterone levels, endocrinologists usually ask the laboratory to measure the amount of free testosterone in the blood. Hormone levels in the body usually vary by time of day (because of internal 24-hour cellular clocks). Researchers who study testosterone recommend that measurements of free testosterone be done early in the morning.

Researchers in Paris and elsewhere in France have conducted a study with 113 HIV-positive men, all less than 50 years old, who did not have AIDS and who were taking ART and who had a viral load less than 50 copies/mL. The researchers published their findings in the January 28, 2017 issue of the journal *AIDS*. They found that about 12% of the men had lower-than-normal levels of testosterone (measured as free testosterone)—less than 70 pg/mL. This rate of low testosterone (called hypogonadism) is double the rate that would be seen in HIV-negative men of a similar range in age.

The researchers stated that they found a link between the use of integrase inhibitors and the

presence of low testosterone. We caution readers that due to the study's design and other issues, such a conclusion must be treated very cautiously, and we explain why the researchers may have inadvertently arrived at such a conclusion.

Study details

The average profile of the men when they were recruited for this study was as follows:

- age – 41 years
- CD4+ count – 627 cells/mm^3
- estimated duration of HIV infection – six years

Bear in mind that blood and other tests were done largely at one point in time. We will return to this aspect of the study later.

Results—Testosterone

- Levels of antibodies that bind to testosterone were elevated in 48% of participants.
- Lower-than normal levels of testosterone were found in 12% of men.
- Men who had low testosterone levels were more likely to have had HIV longer than men with normal testosterone levels.
- Some men with low testosterone levels also had thinner-than-normal bone density.
- Having a percentage of body fat greater than 19% was associated with decreased testosterone levels (excess belly fat can convert some of the body's testosterone into estrogen).

Erectile dysfunction

Men with low testosterone were more likely to have ED. However, even among men with normal levels of testosterone, 54% had ED. Men with ED had been using ART longer (76 months) than men without ED (44 months).

Specific anti-HIV drugs

The researchers stated that they found a relationship between the use of integrase inhibitors for more than two years and the presence of hypogonadism. Note that only 14 men were using integrase inhibitors in this study. We urge readers to treat this finding with caution due to a number of factors, including the nature of the study, which is explained below.

Bear in mind

1. This study's design is cross-sectional in nature; data were captured largely at one point in time. Cross-sectional studies are good at finding associations between a drug and, in this case, a problem (hypogonadism). However, cross-sectional studies by their nature can never prove cause and effect (that is, that integrase inhibitors cause hypogonadism). Cross-sectional studies are a good starting point to begin to explore a research question. If something interesting turns up, it can then be better understood in a study of a more robust statistical design.

2. There were only 14 men who used integrase inhibitors in the French study. This is insufficient for drawing robust conclusions about the impact of this class of medicines on testosterone levels (or anything else). The researchers stated that they were surprised by the association between integrase inhibitors and low testosterone, which is understandable because integrase inhibitors have been in use for about a decade in high-income countries. Also, it is odd that no other team of researchers has found this connection. Furthermore, in other studies, low testosterone has been found in HIV-positive men who were not taking ART and, in men who were taking ART before the introduction of integrase inhibitors.

3. The French researchers stated that they found an association between low testosterone and integrase inhibitors. However, this conclusion could have been skewed by other factors that were unmeasured by their study. For instance, why were some patients given integrase inhibitor–based therapy and others were not? What was the medical history of these patients? Researchers did not apparently screen participants for the presence of all major ED risk factors. Furthermore, the researchers did not address these points in their analysis. It may be that doctors had reasons for prescribing the anti-HIV drugs that they did, and that by chance people with low testosterone just happened to receive integrase inhibitor–based therapy. Such are

some of the problems that can bedevil a cross-sectional study and the conclusions drawn from such studies.

4. What can be reasonably extracted from the present study is the following:

   - free testosterone measurements are useful
   - some HIV-positive men have lower-than-normal levels of testosterone
   - ED is common among HIV-positive men

What needs to be done

The role of HIV treatment on testosterone levels (and ED) needs to be explored in a study of a more robust statistical design. Such a study would have many more participants, but size alone is insufficient to prove cause and effect. Ideally, as part of some randomized clinical trials, men would be screened for risk factors both for ED and low testosterone prior to initiation of ART and monitored while taking anti-HIV treatment. However, large, well-designed studies are expensive. In an era of austerity, it may take time to raise the funds necessary for such a large and well-designed study. The French researchers stated that they are engaged with a larger study to confirm their findings but did not state details as to that larger study's design.

It is good that some researchers, such as the present French team, are interested in studying testosterone levels and why some HIV-positive men might have lower-than-normal levels. The findings from the French study are certainly interesting and should be seen as a beginning and not an end to understanding the issue of low testosterone and ED and their possible causes in HIV-positive men. Hopefully, the French study will stimulate other researchers to conduct further explorations on testosterone, ED and its relationship, if any, with HIV treatment. However, for now, any link between their findings on testosterone and the use of integrase inhibitors must be treated with caution until they are confirmed in a study that is statistically more robust.

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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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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.

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