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I SEXUALLY TRANSMITTED INFECTIONS

A. Researchers study *M. genitalium* in Montreal

Bacteria called *Mycoplasma genitalium* (*M. genitalium* or Mgen) are an emerging sexually transmitted infection (STI). Mgen generally causes symptom-free infection in the urinary tract. However, some people who have this infection can develop urinary problems, including the following:

- discomfort, pain or a burning sensation when urinating
- the need to urinate more frequently than usual
- a sudden need to urinate
- painful intercourse
- painful ejaculation in men
- a discharge from the penis or vagina

These symptoms can be caused by other bacteria, such as those that cause gonorrhea or chlamydia, so a visit to a healthcare provider is necessary to determine the cause of urinary problems.

MG is not commonly diagnosed but it is increasingly being studied, particularly in gay, bisexual and other men who have sex with men (gbMSM).

A team of researchers in Montreal conducted a study called Engage with 716 gbMSM. They collected blood and urine samples as well as swabs of the rectum and throat between November 2018 and November 2019.

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The researchers analysed the collected specimens for Mgen and for the bacteria that cause gonorrhea and chlamydia.

Specimens that tested positive for Mgen were further analysed for the presence of genes that are associated with resistance to commonly used antibiotics, such as the following:

- macrolides (such as azithromycin or clarithromycin)
- quinolones (such as ciprofloxacin or moxifloxacin)

Key findings

Overall, about 6% of participants had Mgen—4% in the rectum and 2% in the urine. Only two participants (0.2%) had Mgen in their throat swabs.

Men who had Mgen were likely to:

- be younger than 29 years
- have had six or more sex partners in the past six months

In general, rates of infection with gonorrhea-causing bacteria were relatively low—about 1.5% of the swabs from the rectum or throat tested positive and none of the urine samples were positive.

Rates of infection with the bacteria that cause chlamydia were low in throat swabs (less than 1%) but higher in urine samples (2%) and rectal swabs (3%).

There were 107 men who had HIV and researchers found that they were not at increased risk for Mgen.

Antibiotic resistance

Analysis found that 46 out of 56 specimens (82%) that tested positive for Mgen had genes that are associated with resistance to macrolides; 16 out of 55 specimens (29%; one specimen could not be assessed for other tests) had genes that are associated with resistance to quinolones. A total of 15 specimens had resistance to both classes of antibiotics.

The researchers noted that the rate of resistance to macrolide antibiotics in the present study is higher than previously reported in other studies in Western Canada or Ontario (63%).

The researchers theorized that the high degree of macrolide resistance in Mgen occurred because these antibiotics were used to treat a wide range of STIs in the past.

For the future

The researchers noted that co-infection with Mgen can occur in gbMSM who also have chlamydia or gonorrhea. They encourage healthcare providers to remain "highly vigilant for a possible co-infection in the case of persistent symptoms after adequate treatment [for gonorrhea or chlamydia]," as routine screening for Mgen is not recommended. This is because most cases of Mgen infection are symptom free and exposure to antibiotics may contribute to the further development of resistance.

The researchers stated that the capacity for Mgen testing in Canada is limited. They added that such testing should occur in patients who have persistent or recurrent symptoms suggestive of Mgen infection. In these cases, the recommended treatment is a course of azithromycin; a secondary choice for treatment would be moxifloxacin.

However, recall that the present study found high rates of resistance to azithromycin and that some participants had Mgen that was also resistant to quinolones. Therefore, the researchers called for rapid access to and turnaround of testing for Mgen and assessment of specimens for the presence of resistance to commonly used antibiotics.

The researchers also called for "easier and quicker access" to alternative antibiotics, such as pristinamycin, for the treatment of Mgen. Currently, access to pristinamycin is through Health Canada's Special Access Program (SAP).

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II ANTI-HIV AGENTS

A. Emerging experimental treatment – bictegravir + lenacapavir

Biktarvy is a pill containing the following anti-HIV drugs:

- bictegravir – an integrase inhibitor
- FTC (emtricitabine) – a nucleoside analogue
- TAF (tenofovir alafenamide) – a nucleoside analogue

The combination of drugs in Biktarvy is generally well tolerated and effective against HIV. Biktarvy is a complete regimen in a pill and is taken at a dose of one pill daily with or without food.

Reducing exposure to drugs

Until there is a cure, people with HIV will have to take treatment on a regular basis in order to keep the virus suppressed and stay healthy. Since 1996, the standard of care has been a combination of three drugs. Back then, attempts at reducing the burden of medicines taken by people with HIV failed largely because treatments used were not as effective as those that are available today.

In the past five years, the pharmaceutical company ViiV Healthcare has developed regimens consisting of two drugs that have proven to be highly effective in clinical trials. The first pill containing a two-drug regimen was Juluca—dolutegravir + 3TC (lamivudine). The second pill containing another complete regimen was Dovato—dolutegravir + 3TC.

Subsequently, ViiV developed another regimen, a long-acting injectable called Cabenuva that consists of two drugs—cabotegravir + rilpivirine.

Given the lifelong burden of HIV treatment, it is plausible that a two-drug regimen may be beneficial.

Lenacapavir

The pharmaceutical company Gilead Sciences (maker of Biktarvy, TAF and FTC) has developed lenacapavir (Sunlenca), which belongs to a class of drugs called capsid inhibitors.

After initial oral dosing for approximately two weeks, lenacapavir can be injected every six months. It was originally developed to be part of combination therapy with other drugs taken orally, as there is currently no drug with which it can be partnered for injection every six months. As it has to be injected over the long term and currently available drug combinations work for most people, lenacapavir is reserved mainly for highly treatment-experienced people who have HIV that is resistant to several drugs. In other words, it is not a commonly used HIV treatment.

Bictegravir + lenacapavir

Spurred by the success of other two-drug regimens, Gilead is developing a two-drug regimen consisting of bictegravir + lenacapavir, to be taken orally.

A clinical trial (NCT 05502341) with this combination is underway in several countries in people with HIV. Participants recruited for this study have been taking a complex regimen either because of a history of drug-resistant HIV or because they have an intolerance to some other therapies (and therefore reduced treatment options).

The trial has a complex design, but after a two-day loading dose of lenacapavir, most participants will get a combination of bictegravir at a dose of 75 mg per day with lenacapavir dosed at 25 mg or 50 mg per day. The remaining participants will remain on their pre-study regimen.

If the combination of bictegravir + lenacapavir is successful, it will likely be approved for treatment. The combination could become an option for people with multidrug-resistant HIV or for people whose doctors want to prescribe a nucleoside-free regimen.

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B. A potential long-acting treatment – GS-1614

The Calibr-Skaggs Institute for Innovative Medicines in La Jolla, California, conducts early-

stage research with potential treatments for different infectious diseases.

Calibr has developed a potential HIV treatment code-named GS-1614 that has been licensed to Gilead Sciences for further development. Gilead will conduct studies of GS-1614 to better understand its safety and effectiveness as a potential treatment for HIV.

About GS-1614

GS-1614 is a pro-drug. Pro-drugs are medicines that are in one form but once taken into the body (either by pill or by injection) they are converted into an active drug. In the case of GS-1614, it is converted within the body to a drug called islatravir.

Islatravir belongs to a class of drugs called NRTTIs (nucleoside reverse transcriptase translocation inhibitors). Although this class of drug is relatively new (it was first discovered about a decade ago), islatravir has potent anti-HIV activity. It interferes with an enzyme used by HIV-infected cells called reverse transcriptase. It also interferes with HIV's ability to take over an infected cell. It is possible that there may be other ways that islatravir works against this virus.

Perhaps most importantly, GS-1614 (and islatravir) have the potential to become long-acting treatments. The pharmaceutical company Merck is developing islatravir for clinical use. Gilead will cooperate with Merck to develop GS-1614 in combination with lenacapavir so that a dual long-acting regimen can be tested.

However, before that can happen, extensive research is needed to confirm the safety of GS-1614. In previous studies, Merck found that islatravir caused a temporary decrease in a group of cells called lymphocytes (commonly called B- and T-cells) in the blood of some people who used high doses of this drug. Subsequent clinical trials of islatravir are using much lower doses. Hopefully, the doses of GS-1614 selected for research in people will be sufficiently low that they do not cause this problem.

It is still too early in the development program for GS-1614 to determine if it will be successful. However, it is possible that within the next five years a combination of GS-1614 and lenacapavir could become an option for a long-acting HIV treatment, perhaps given every six months.

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III WEIGHT ISSUES

A. Higher physical activity levels linked to less belly fat

Thanks to the power of HIV treatment (antiretroviral therapy, ART), researchers predict that many ART users will live long and healthy lives, well into their senior years. However, as everyone ages, regardless of HIV status, issues associated with aging begin to appear. These can include high blood pressure, diabetes, cardiovascular disease and, in some cases, weight gain.

It is normal for people to gain some weight as they grow older—they may engage in less physical activity, metabolism slows down and there are hormonal factors as well. To counter this, increased aerobic exercise, building muscle mass and implementing dietary changes may be necessary. Compared to studies of pills or injections, there are far fewer well-designed studies on the effect of exercise in people with HIV. Such non-pharmaceutical studies are complex and not prioritized for scarce research funds.

Despite this, a team of researchers at the University of Washington (in Seattle) and several other academic-medical centres in the U.S. conducted a short-term (about one week) study using wearable high-precision devices (accelerometers) that measured physical activity in participants.

In analysing the data from 419 participants with HIV, researchers found that people who were physically active (more steps per day) tended to have the least amount of belly fat. The converse was also true—people who had the least amount

of physical activity had the greatest amount of belly fat.

The researchers encouraged the development of studies to find the right amount of exercise needed to help people minimize their belly fat.

The fat that is deposited deep in the belly is called visceral fat. This fat wraps itself around organs and over the long term can contribute to poor health. Exercise has many benefits, including the following:

- it releases chemical signals that can help burn stored fat
- it enhances mood and memory
- it is good for cardiovascular health

Building up muscle is important because as people age they tend to lose muscle. Muscle helps maintain overall health and can burn fat. In addition, by engaging in more physical activity people can build up their endurance and ability to carry out desired everyday activities.

Study details

Researchers recruited participants from the following cities:

- Boston, MA
- Birmingham, AL
- Cleveland, OH
- Seattle, WA

Study staff used simple time-tested ways to estimate belly fat, including measuring waist size and the waist-to hip-ratio.

Physical activity was measured with the ActiGraph accelerometer. Participants wore this device while awake (except for when bathing or swimming) for at least 10 hours per day, for between seven and 10 days.

The average profile of participants was as follows:

- 58 years
- 23% female, 77% male
- major ethno-racial groups: Black – 54%; White – 44%
- years taking ART – 14
- most participants were taking regimens based on an integrase inhibitor (such as bictegravir, dolutegravir or elvitegravir)
- body mass index (BMI) – 28 kg/m^2
- co-morbidities: high blood pressure – 77%; reduced kidney function – 40%; diabetes – 33%; cardiovascular disease – 22%

Results

On average, participants took nearly 5,000 steps per day. Researchers found that almost 55% of participants did either 150 minutes per week of moderate-to-vigorous physical activity or 75 minutes per week of vigorous physical activity.

Researchers took into account factors such as sex, employment, age and so on when further analysing their data. They found that the more steps a person walked each day, the more likely they were to have a smaller waist. The researchers found that the time participants spent on moderate-to-vigorous physical activity was not linked to waist size.

The researchers recommended that healthcare providers assess patients' physical activity and prescribe exercise, such as the following:

- join a walking group
- undergo supervised exercise training
- join a community exercise program

For the future

The present study should be seen as building a foundation for a research program. Next up are longer studies to assess the impact of different types of physical activity and their duration and intensity on belly fat in people with HIV. Such studies can yield targeted recommendations for different people.

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