TreatmentUpdate 245

Vol. 34, No. 2 · March/April 2022

Available online at
www.catie.ca/treatmentupdate

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I SEXUALLY TRANSMITTED INFECTIONS

A. Shrinking options for antibiotics in gonorrhea

Gonorrhea is a common sexually transmitted infection (STI). It can cause inflammation of affected tissue—usually in the anogenital tract and throat. Gonorrhea can contribute to pelvic inflammatory disease in women, can lead to infertility and can be transmitted to an infant during pregnancy, leading to blindness.

In the early 20th century, the treatment for gonorrhea was initially sulpha drugs and later penicillin. However, the bacteria that cause gonorrhea (*N. gonorrhoeae*) eventually developed resistance to these drugs. Subsequent oral antibiotics were developed and used to treat gonorrhea, but N. gonorrhoeae has developed reduced susceptibility or, in some cases, resistance to them. Below is a brief history of gonorrhea treatments in the United States—when they were introduced and when the development of significant resistance occurred (broadly similar trends happened in Canada and Europe around the same period):

- Sulpha drugs were introduced in the 1930s and failed in many cases by the mid-1940s.
- Penicillin was introduced in the mid-1940s and was no longer recommended by 1989.
- Spectinomycin was introduced in 1961 and began to fail in the 1980s.

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- Ciprofloxacin and similar drugs were introduced in the early 1980s and were no longer recommended by the end of that decade.
- Azithromycin was introduced in the early 1990s and was no longer recommended by 2007 (as single-drug therapy).

Ceftriaxone was introduced about 40 years ago and has been an important antibiotic for serious infections of the abdomen, lungs, brain and other tissues. As other antibiotics encountered increasing resistance from gonorrhea-causing bacteria, ceftriaxone began to be used more frequently. Today, ceftriaxone is the leading antibiotic for gonorrhea treatment in Canada and many high-income countries. Ceftriaxone is given as a single dose by intramuscular injection in many countries, and in Japan and China via intravenous infusion.

Increasing doses

Over the past 40 years, gonorrhea-causing bacteria have become less susceptible to ceftriaxone. For instance, in the early 1980s, clinical trials found that a single dose of 125 mg of ceftriaxone was able to cure gonorrhea. However, by 2022, doses of 500 mg were being routinely used in the U.S. What's more, even higher doses—1,000 mg—were recommended in Europe and Japan. In some parts of China, researchers have documented extremely high doses of ceftriaxone (greater than 1,000 mg) being used for gonorrhea treatment.

Given the historical trend of how gonorrhea-causing bacteria respond to antibiotics, it is possible that in the future *N. gonorrhoea* may require even higher doses of ceftriaxone or longer courses of this drug than what is routinely used in Europe or North America. Reports of resistance to ceftriaxone by gonorrhoea-causing bacteria remain rare but have been slowly increasing in the past decade. It seems obvious that new antibiotics for the treatment of gonorrhea (and other bacteria) are needed, but it is not clear if candidate treatments currently in late-stage clinical trials will be successful and achieve regulatory approval. For instance, two antibiotics—delafloxacin and solithromycin—once considered promising candidates for gonorrhea treatment, yielded disappointing clinical trial results in the past decade.

Antibiotic development

According to a report of antibiotic development commissioned by the Biotechnology Innovation Organization (BIO), most antibiotics (82%) approved by regulatory authorities were developed prior to the year 2000. The report states that most of these antibiotics "are facing eventual loss in efficacy due to resistance developed by bacterial strains encountering these treatments in the population. For the next generation of [antibiotics] to fill the gap, there needs to be a well-funded and appropriately rewarded biotech ecosystem for translational science to reach the clinic and beyond."

Underfunded

The BIO report found that over the past decade, antibiotic development programs were only able to raise US $2.3 billion. In the same decade, companies working on the development of anticancer drugs were able to raise US $38 billion. Not surprisingly, there are now fewer clinical trials of antibiotics compared to about a decade ago.

Reasons for the insufficient funding

Most new clinical drug development is done by the pharmaceutical industry. However, the BIO report found that large companies have been leaving the field of antibiotic development. This appears to be driven by poor prospects of profitability for new antibiotics.

Some other key findings from the BIO report are as follows:

- Most antibiotics have lost patent protection and are now relatively cheap generic drugs.
- New powerful antibiotics will probably be reserved for limited use, perhaps primarily in hospitals. Patients may only get new antibiotics if treatment with older ones fails.
- If approved, new antibiotics will likely only be used for a relatively short period of time (in each person). Furthermore, hospitals may ration their use in an attempt to preserve their efficacy.
- Pharmaceutical companies, being for-profit corporations, will generally want to maximize the price of new antibiotics, while public drug formularies (that subsidize the cost of medicines and have limited budgets) will want to pay lower prices.

The *New York Times* has noted that in the past five years, financial issues have dogged some companies that focused on antibiotic development. For instance, three biotech companies that were developing antibiotics have had to file for bankruptcy and/or creditor protection because of disappointing results from clinical trials and/or sales revenue.

These and other factors have had a negative impact on the scale of development of new antibiotics. A recent report by a team of scientists from several countries has largely arrived at similar conclusions to the BIO report. Although antibiotics are in development, some scientists have noted that many of the ones in late-stage clinical trials are not truly innovative but analogues of existing antibiotics. As they are analogues, they may not be effective against all strains of bacteria resistant to existing antibiotics.

Perhaps innovative models for funding and eliciting interest in antibiotic development are needed. Such models could include intensified partnerships that involve governments, universities, foundations and the private sector.

A global threat

Research by scientists who study the ability of germs to resist treatment—this ability is called antimicrobial resistance (AMR)—suggests that worldwide about five million people died in 2019 because of drug-resistant germs. What's more, research commissioned by the government of the UK suggests that drug-resistant microbes could kill as many as 10 million people each year by 2050. Many of these deaths would be caused by drug-resistant bacteria.

To help prevent further deaths from drug-resistant bacteria, scientists and policy makers will need to deploy a combination of the following strategies:

- community-based programs to ensure access to sanitation and clean water
- developing vaccines to prevent key bacterial infections
- reducing unnecessary use of antibiotics
- increasing funding for the development of new antibiotics

Back to gonorrhea

Although there are at least two experimental antibiotics—zoliflodacin and gepotidacin—in phase III clinical trials for gonorrhea treatment, these trials may not be finished until mid-to-late 2023. The data collected then have to be analysed and submitted to regulatory authorities for their review and hopefully approval. Thus, even if these drugs are found to be generally safe and effective for gonorrhea treatment, they may not be available until 2024.

In the meantime, based on lab experiments with gonorrhea-causing germs and antibiotics, some researchers have proposed that older antibiotics approved for other infections or other classes of drugs approved for other conditions be repurposed and tested in clinical trials for their potential to treat gonorrhea. Such drugs include the following:

- acetazolamide
- lefamulin (Xenleta)
- ertapenem (Invanz)
- ertapenem + moxifloxacin
- gentamicin + moxifloxacin

The next report in this issue of *TreatmentUpdate* is about a clinical trial that compared the effectiveness of different antibiotics primarily for the treatment of anogenital gonorrhea.

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B. Ertapenem seems similar in effectiveness to ceftriaxone for gonorrhea

The use of penicillin in the mid-1940s ushered in the era of powerful antibiotic therapy for a wide range of infections, including gonorrhea and syphilis. However, since that time, the bacteria that cause gonorrhea have been evolving the ability to resist first penicillin and subsequently other antibiotics.

As new antibiotics are not currently being developed at the same pace as they once were, scientists are reassessing older antibiotics approved for other conditions that have the potential to be repurposed as a treatment for gonorrhea.

About ertapenem

One older antibiotic that is very promising as a potentially repurposed treatment for gonorrhea is ertapenem (Invanz). This antibiotic was approved in Canada and other high-income countries about 20 years ago. It is used for the treatment of complicated abdominal, bone, brain, lung and pelvic infections, as well as for diabetic foot infections. Ertapenem can be administered both

intravenously or via intramuscular injection in Canada and some other countries. For most infections in adolescents and adults, the usual dose is 1 gram per day for between five and 14 days. In the case of diabetic foot infections, the manufacturer, Merck, recommends a course of treatment that lasts between five and 28 days.

About 20 years ago, Merck facilitated the lab research to understand ertapenem's effect on gonorrhea-causing bacteria. These experiments suggested that the drug was able to inhibit the growth of more than 600 isolates of gonorrhea-causing bacteria. Some of these bacteria were resistant to ciprofloxacin and ertapenem was active against these drug-resistant strains.

However, at the time these experiments were done, relatively low doses of ceftriaxone and another antibiotic, cefixime (taken in pill form), could be used to treat gonorrhea and were highly effective. Also, another antibiotic, azithromycin (which could also be taken in pill form) was also in use and largely still effective against gonorrhea (and syphilis). So ertapenem was bypassed in favour of these other drugs.

A clinical trial in the Netherlands

Recently, Dutch researchers published the results of a randomized, double-blind controlled trial in adults with uncomplicated gonorrhea (primarily anorectal and urogenital gonorrhea). The study, called Nabogo, tested the following antibiotics:

- ceftriaxone – 500 mg given as a single dose via intramuscular injection
- ertapenem – 1,000 mg given as a single dose via intramuscular injection
- gentamicin – 5 mg/kg of body weight (to a maximum of 400 mg) given as a single dose via intramuscular injection
- fosfomycin – 6 grams in a solution that was swallowed

Some participants also received placebo injections or placebo oral solution.

The researchers asked 2,160 people who had been diagnosed with gonorrhea to participate in the study. However, only 346 (16%) agreed to participate.

As ceftriaxone is the standard of care for gonorrhea, the effects of the other antibiotics were compared to it.

The researchers found that ertapenem was neither worse nor better than ceftriaxone (the technical statistical term used to describe this outcome is "non-inferior"). Gentamicin had a similar result, but there are concerns about its use. Fosfomycin proved to be poorly effective, and recruitment and assignment to this drug in the trial was quickly halted. Issues related to gentamicin and fosfomycin are discussed later in this report.

Although the study was small, it found that ertapenem was highly effective and should be studied in a larger trial.

Study details

Researchers with the Public Health Service in Amsterdam recruited people who tested positive using an assay that assessed their sample (urine or swabs of affected tissue) for the genetic information of the bacteria that causes gonorrhea. People who were immune suppressed were not recruited; this would have included people who were taking transplant medicines or HIV-positive people with a CD4+ count less than 200 cells/mm^3.

The distribution of participants was as follows:

- ceftriaxone – 103 people
- ertapenem – 103 people
- gentamicin – 102 people
- fosfomycin – 38 people

The study was done between September 2017 and June 2020. Research staff administered the medicines; in the case of fosfomycin, they observed participants drinking the drug.

Most participants (90%) were gay, bisexual or other men who have sex with men (MSM). A total of 71 participants had HIV.

Among 272 HIV-negative people, 32% were using HIV pre-exposure prophylaxis (PrEP).

Between one and two weeks after initiating treatment, participants returned to the study clinic to have urine samples or swabs collected and analysed to find out if they were cured.

Participants were told to avoid sex until the study lab could confirm that they were cured. If they did have sex, they were encouraged to use condoms.

Participants kept diaries during the study to keep track of any adverse effects of treatment and any sexual activity.

Lab analysis found that all participants had gonorrhea that was susceptible to ceftriaxone.

Results

The proportions of people cured of anogenital gonorrhea were as follows:

- ceftriaxone – 100%
- ertapenem – 99%
- gentamicin – 93%
- fosfomycin – 12%

Focus on the throat

Researchers were primarily interested in the ability of one course of treatment to eradicate gonorrhea from the anorectal or urogenital site. Some people had detectable gonorrhea in more than one place, for example, the anorectal region and the throat.

The researchers noted that the eradication of gonorrhea from the throat is more difficult than from other parts of the body. As a result, they decided to assess eradication of gonorrhea from the throat as a secondary (or less important) aim of the study.

The researchers stated that the ideal duration of time between initiation of treatment and getting a swab from the throat to assess if gonorrhea was cured there is not clear. In the study, this duration was between one and two weeks. It is possible that a longer duration may have been needed.

The proportions of people who had gonorrhea of the throat cured were as follows:

- ceftriaxone – 90% (38 out of 42 people) cured
- ertapenem – 88% (29 out of 32 people) cured
- gentamicin – 26% (9 out of 38 people) cured

Note: As mentioned earlier, fosfomycin proved to be poorly effective and recruitment and assignment to receive this drug in the trial were quickly halted. Issues related to gentamicin and fosfomycin are discussed later in this report.

Side effects

Antibiotics can cause temporary episodes of diarrhea, as they cause a shift in the balance of bacteria in the gut.

Diarrhea was reported by participants who received fosfomycin (87%), ertapenem (50%) and ceftriaxone (11%); it was rare in people who used gentamicin (2%).

One person who received ertapenem developed tightening of his throat. This was interpreted as an allergic reaction and he was given antihistamines in the emergency department of a hospital. He recovered.

In 14 participants the researchers noted "clinically relevant" declines in a measure of kidney health called eGFR (estimated glomerular filtration rate). That is, eGFR values declined by more than 25% in these people, more or less evenly distributed among the study medicines. However, none of the decreases in eGFR were deemed severe and most of the people recovered within a few weeks.

Focus on fosfomycin

The dose of fosfomycin used in the study was 6 grams in a single oral dose. However, this drug generally failed to cure participants of gonorrhea. As researchers noticed this partway through the study, they stopped recruiting people and assigning them to receive fosfomycin long before the overall study was completed.

The researchers stated that, based on past studies, it is plausible that fosfomycin taken repeatedly for several days might be able to cure people of gonorrhea. However, it is clearly not useful as a single-dose regimen. The researchers were interested in exploring single-dose regimens in the present study for ease of administration. Other researchers have found that not everyone who requires multiple treatments and assessments for sexually transmitted infections returns for further care and treatment. Such behaviour could lead to the spread of drug-resistant bacteria. Hence the focus on a single dose of treatment for gonorrhea in the present study and in most ongoing studies.

Focus on gentamicin

In a previous study, the combination of 240 mg of gentamicin with 1 gram of azithromycin was not as effective as the combination of ceftriaxone-azithromycin for gonorrhea clearance.

In the present study where the dose of gentamicin was adjusted by weight, participants received between 280 to 400 mg of this drug. However, the researchers found that despite this higher dose (compared to the one used in a previous study), gentamicin was inadequate for treatment of gonorrhea of the throat.

It is plausible that giving higher doses or longer courses of gentamicin could be more effective. However, the researchers cautioned that doing so "will probably increase the risk for serious [toxicity]." Gentamicin can injure the inner ears and kidneys.

Recruitment

The researchers stated that "a substantial proportion of eligible individuals declined to participate." Many people who chose not to participate cited causes that inconvenienced them or interfered with their routines. Such causes included long wait times at the study clinic and/or having to make multiple study visits.

For the future

The present study, though well designed, was relatively small. The Dutch researchers stated that based on their results, ertapenem "might provide an alternative option for ceftriaxone susceptible gonorrhea." There are many issues about the Nabogo trial to consider and these are discussed in the next report in this issue of *TreatmentUpdate*.

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C. Issues to consider about repurposing ertapenem

As reported earlier in this issue of *TreatmentUpdate*, Dutch researchers have found preliminary evidence that the antibiotic ertapenem has the potential for use as a treatment for gonorrhea. However, the Dutch trial, code-named Nabogo, was relatively small and had limitations. These limitations must be kept in mind when planning future research with ertapenem as a treatment for gonorrhea.

Ceftriaxone susceptibility

Lab testing in the Dutch study confirmed that all strains of gonorrhea in participants were susceptible to ceftriaxone. Over the past two decades, there have been increasing reports of cases of gonorrhea resistant to ceftriaxone. Will ertapenem work against such strains?

A decade ago, scientists in Sweden conducted lab experiments with four strains of gonorrhea that were resistant to ceftriaxone. They found that ertapenem was able to stop the growth of these four strains of gonorrhea-causing bacteria. Note that as promising as these test-tube results are, they require confirmation in a clinical trial with people who have gonorrhea resistant to ceftriaxone. Many lab experiments that seem promising do not always have the same results when tested in people. Also, in cases of ceftriaxone-resistant gonorrhea, it may be necessary to use doses of ertapenem that are higher than what was used in the present Dutch study. It is even plausible that multiple doses of ertapenem (rather than a single dose) might be required for the treatment of ceftriaxone-resistant gonorrhea. These are issues that could be explored in future clinical trials.

Women

The proportion of women in the Dutch trial was small, limiting its relevance to this population.

Furthermore, one woman with cervical-vaginal gonorrhea was not cured when treated with ertapenem. More research needs to be done with ertapenem in this population.

Throat infection

Gonorrhea in the throat can be difficult to cure, perhaps because antibiotics have difficulty reaching high concentrations in throat tissue. The main purpose of Nabago was to assess the effectiveness of treatment on anorectal or urogenital gonorrhea. A minority of participants had gonorrhea in the throat. Among these people, most who were treated with ceftriaxone (90%) or ertapenem (88%) were cured.

This finding is promising, but the Dutch researchers called for more randomized trials to assess the ability of antibiotics to cure gonorrhea in the throat.

Other issues

Participants in Nabago had uncomplicated gonorrhea. Future studies need to assess ertapenem's effectiveness at treating gonorrhea-causing bacteria that has spread to tissues beyond the anogenital and urogenital tracts and/or throat. This is called disseminated gonorrhea.

It is possible that ertapenem could be used in combination with another antibiotic in a clinical trial to enhance its effect on gonorrhea or to help wipe out coinfections (such as chlamydia or *Mycoplasma genitalium*). However, additional research is needed to select a drug that could fulfill such a potential role.

Cost

The Dutch researchers stated that "the costs of ertapenem are considerably higher than ceftriaxone." This may limit its potential use against gonorrhea in the future.

Recruitment

Nabago encountered challenges in recruitment. Such challenges may bedevil future clinical trials for antibiotics that target gonorrhea and may therefore slow the pace of research.

Reserved for rescue

Due to some of the previously mentioned issues, it is likely that, for the foreseeable future, clinics and hospitals will reserve the use of ertapenem in cases where ceftriaxone has failed.

Although the Dutch study is an important step forward, research remains to be done to uncover ertapenem's full potential against gonorrhea and to determine the best dose and duration of therapy.

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D. High-dose ceftriaxone for gonorrhea in Japan

As mentioned earlier in this issue of *TreatmentUpdate*, in the past two decades, gonorrhea has become less susceptible to several antibiotics, including ceftriaxone, the standard of care for gonorrhea today. Although cases of ceftriaxone resistance are relatively rare in Europe and North America, it seems likely that in the years ahead it may become more common.

Raising the dose

Ceftriaxone is the preferred treatment for gonorrhea in Canada and many high-income countries. To ensure its success in treating gonorrhea, public health authorities in many countries and regions have increased the recommended dose for adults and adolescents with uncomplicated gonorrhea as follows:

- Japan – 1 gram given as a single intravenous dose
- Europe – 1 gram given as a single intramuscular injection with 2 grams of azithromycin taken orally
- United States – 500 mg given as a single intramuscular injection
- United Kingdom – 1 gram given as a single intramuscular injection

At press time, the preferred treatment for gonorrhea in Canada was ceftriaxone 250 mg given as a single intramuscular dose, accompanied by another antibiotic, azithromycin, given in pill form also as a single dose. Given that reports suggest that azithromycin-resistant gonorrhea is spreading across Canada, it is likely that at some point in the future guidance for gonorrhea treatment will be updated.

In Japan

In Japan, ceftriaxone is administered via intravenous infusion when used for gonorrhea treatment, while in North America and Western Europe this drug is usually given via intramuscular injection. Japanese researchers cited data from the 1990s that suggest that when 1 gram of ceftriaxone is administered via intramuscular injection or intravenously, the result is that levels in the blood are similar.

Researchers in Tokyo have been investigating the impact of different antibiotic regimens for the treatment of gonorrhea. The researchers were interested in the ability of antibiotics to cure gonorrhea in the throat and rectum. They compared the following regimens:

- ceftriaxone – 1 gram given intravenously as a single dose
- ceftriaxone – 1 gram given as above along with either of the following antibiotics taken orally: azithromycin 1 gram (also as a single dose) or doxycycline 100 mg twice daily for seven consecutive days

The combination regimen was used in cases where both gonorrhea and chlamydia were diagnosed.

The researchers recruited 320 people—208 of whom were given ceftriaxone alone and 112 of whom were given combination therapy with ceftriaxone and an oral antibiotic.

In comparing the two regimens, the researchers found no differences in rates of cure.

Later in this report we highlight some issues with the study.

Study details

Researchers enrolled 320 participants, all of whom were gay, bisexual or other men who have sex with men (MSM). The men underwent screening for gonorrhea of the throat and/or rectum and for chlamydia. Visits to the study clinic were done every three months between 2017 and 2020.

Participants returned to the study clinic at least two weeks after they received treatment to have swabs done to check if gonorrhea and/or chlamydia was cured.

All gonorrhea infections were symptom free.

On average, the men were 30 years old (ranging between 18 and 57 years).

Results

Researchers found that both regimens were highly effective, with 98% of participants cured with ceftriaxone alone and 96% cured with combination therapy. This difference in cure rates was not statistically significant.

Cure rates did not differ whether gonorrhea was in the throat or the rectum.

Treatment failure

Treatment for gonorrhea failed in nine cases, distributed as follows:

- ceftriaxone alone – four cases: three in the throat and one in the rectum
- ceftriaxone + oral antibiotic – five cases: three in the rectum and two in the throat

In all nine cases, researchers analysed the genetic information from strains of gonorrhea isolated from the men. The researchers were not able to find genetic markers of resistance to ceftriaxone in any of these cases. They therefore re-treated all the men with another round of ceftriaxone (without any oral antibiotics) at a dose of 1 gram given as a single intravenous dose.

Subsequently, the researchers found that eight of the nine men were cured. Again, investigation found that the ninth man did not have ceftriaxone-resistant gonorrhea, so he was given a third course of this drug and was cured.

Adverse events

In general, intravenous ceftriaxone seemed to have been well tolerated, with only one person developing an allergic reaction (graded as moderate intensity by the researchers). This occurred two hours after his infusion. The man was successfully treated with oral corticosteroids and recovered.

Bear in mind

This was not a randomized clinical trial and its findings are not definitive; however, the study is still important, as it compared two regimens. Despite its limitations, this study suggests that 1 gram of ceftriaxone with or without oral antibiotics is, in most cases, effective at treating gonorrhea.

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E. Extremely high doses of ceftriaxone for gonorrhea in some parts of China

Doctors at a hospital in Hangzhou, China, conducted a study screening for drug-resistant gonorrhea for six months in 2019. During that time, they analyzed 70 samples/swabs from people with gonorrhoea. Among these 70 people, seven (10%) had high-level resistance to ceftriaxone and 37% had resistance to another drug, cefixime. The latter drug is taken orally, but in the current era it is not the preferred treatment for gonorrhea in many countries because of resistance.

Prior to seeking care at the hospital, all seven patients (six men, one woman) had been treated with derivatives of penicillin (called cephalosporins), but this therapy had failed. These antibiotics were all structurally related to ceftriaxone, hence the high-level resistance to this latter antibiotic.

To overcome high-level resistance to ceftriaxone, doctors treated four of the seven people with a high dose of ceftriaxone: 2 grams given intravenously for one or two days. Three of them were subsequently cured. The fourth person was retreated with another course of ceftriaxone but did not return to the hospital for a checkup to see if he was cured. The remaining patients were treated with other antibiotics. One person was given a 12-day regimen of cefuroxime (Ceftin) and was cured. Two other patients were treated with other antibiotics; however, they did not return to the hospital for a checkup, so doctors were unable to find out if they were cured.

The seven people were infected with a strain of gonorrhea that has also been found in Europe, Japan, North America and other parts of China.

The importance of this study is at least as follows:

- It documents that higher doses of ceftriaxone than those used in North America or Europe are being prescribed in parts of China for the treatment of gonorrhea.
- Treatment with high-dose ceftriaxone was extended beyond a single dose for some people.
- It showed that the same strains of gonorrhea-causing bacteria can spread to people on different continents.

The use of high doses of ceftriaxone in Hangzhou is not an anomaly, as explained below.

A review in Beijing

In another study, doctors in Beijing reviewed records collected from seven hospitals in five provinces between 2013 and 2017. They focused on 1,686 people who had been diagnosed with gonorrhea. On average, throughout the study, 10% of samples were resistant to ceftriaxone, according to lab tests. A total of 1,401 participants received intravenous ceftriaxone as treatment. Most people in the study received doses of 1,000 mg or greater, as a single dose. Commonly administered doses included the following:

- 2,000 mg
- 3,000 mg
- 4,000 mg
- 6,000 mg

All of these were given intravenously. There were no reports of treatment failure throughout the study period. The doctors thought that the lack of treatment failure occurred because all participants were treated with extremely high doses of ceftriaxone. The Beijing doctors noted that these doses of ceftriaxone are higher than what is recommended for routine use in Chinese guidelines for sexually transmitted infections. The doctors advanced the following reasons for the use of very high-dose ceftriaxone:

- Most ceftriaxone produced for the Chinese market comes in doses of 1,000 and 2,000 mg.
- "There is a sense from most clinicians that domestically manufactured ceftriaxone is less potent than the drug manufactured in other nations, which may have prompted the decisions to give higher doses when prescribing domestically produced ceftriaxone."
- "Patients who were previously diagnosed with *N. gonorrhoeae* or other sexually transmitted infections would be prescribed higher ceftriaxone dosage than those with primary infections in this study."
- "Patients who were already using antibiotics for their infection [at the time they sought care at the hospitals] would be prescribed a higher dosage of ceftriaxone than those who did not use antibiotics at initial presentation. The physicians probably regarded these patients as experiencing clinical treatment failure, so they would prescribe a high dosage."

The Beijing doctors warned that the safety of using such high doses of ceftriaxone is not known. In addition to the treatment of gonorrhea, ceftriaxone is also used for serious bacterial infections of the abdomen, bone, brain, lungs, skin, urinary tract and so on. The most recent Canadian prescribing information for ceftriaxone notes that "there is limited experience with daily doses of 3 to 4 grams administered as a single dose or two equally divided doses. The total daily dose should not exceed 4 grams."

Another consequence of using such high doses as reported in China is the effect on the balance of gut bacteria. It is plausible that excessive doses of ceftriaxone (or other antibiotics) could lead to the overgrowth of bacteria that can cause serious infections in people. However, doctors were not able to assess this possibility in their study.

Historically, strains of gonorrhea or other sexually transmitted infections resistant to antibiotics do not stay in one region but eventually spread throughout the world. Gonorrhea that has become used to extremely high doses of ceftriaxone in parts of China may spread and become harder to treat in other countries where much lower doses of ceftriaxone are used.

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F. Ontario intervention increases detection of syphilis

Over the past 20 years in Canada and other high-income countries, rates of new diagnoses of syphilis have increased among gay, bisexual and other men who have sex with men (MSM), including some who are HIV positive.

Syphilis can cause a complex multistage disease, affecting many organ-systems. Because syphilis is a relatively common sexually transmitted infection (STI), sexually active people need regular screening. Early detection and treatment can help ensure that complications relating to syphilis are minimized and that the disease does not spread.

A team of leading researchers in Ontario conducted a study among four large HIV clinics in Toronto and Ottawa, cities with relatively high rates of syphilis. The researchers compared two interventions in their study:

- Whenever HIV-positive men gave blood samples to assess their viral loads, syphilis screening was also done.
- The usual syphilis testing practices were done—that is, screening for syphilis was triggered by the patient reporting (or the doctor noticing) signs/symptoms typical of syphilis; a request for such testing by the doctor or patient; the patient disclosing to their physician sexual activity that warranted testing, and so on.

The study was done between February 2015 and July 2017. During this time, all four clinics initially engaged in the usual syphilis testing practices; gradually, over the course of the study, one clinic at a time shifted to screening for syphilis whenever HIV viral load testing was done.

Nearly 4,000 men with HIV took part in the study.

Over the course of the study the following occurred:

- There was a 25% increase in detection of early-stage syphilis.
- On average, each participant had at least two syphilis tests each year.
- The number of patients who received a syphilis test at least once per year increased fourfold.

Having syphilis screening as a routine part of testing was perceived by participants as a good thing for the following reasons:

- convenience
- reduced stigma around STIs
- reduced risk of missed opportunities for syphilis screening

For the future

Computer simulations suggest that syphilis screening every three months would likely improve the ability of doctors and nurses to detect cases of early syphilis and interrupt transmission of the germ that causes syphilis. The present study was not designed to elicit such frequent testing, but it has started doctors and their HIV-positive patients on the path toward regular syphilis testing. According to the Ontario team of researchers, in order to achieve syphilis screening every three months, additional interventions will be required, including the following:

- "improved diagnostics that allow for self-testing"
- "virtual and express testing" – patients can obtain lab requisition forms for syphilis testing via a smartphone or computer rather than having to first visit a doctor
- reminders that are sent to patients about the need for frequent testing

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Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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ISSN 1181-7186 (print)
ISSN 1927-8918 (online)

Production of this document has been made possible through a financial contribution from the Public Health Agency of Canada. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada.

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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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