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## I SEXUAL HEALTH

### A. British Columbia researchers find cases of LGV are on the rise

LGV (*lymphogranuloma venereum*) is a sexually transmitted infection (STI) caused by a subtype of chlamydia. Before 2003, reports of LGV were rare in high-income countries. However, that year an outbreak was first reported in the Netherlands among gay, bisexual and other men who have sex with men (gbMSM). The outbreak then spread through sexual networks to other European countries and, shortly after, to Canada and the United States.

Those cases of LGV were associated with the following symptoms:

- anal/rectal ulcers
- painful bowel movements
- painfully swollen lymph nodes in the groin

Some men who developed anal/rectal ulcers related to LGV also developed symptoms such as fatigue, fever/chills and weight loss.

If left untreated, people with LGV-related anal ulcers can develop scar tissue that narrows the anus. Lymphatic vessels can also become scarred, leading to other problems.

LGV can be successfully treated with antibiotics.

### In British Columbia

A team of researchers at the British Columbia Centre for Disease Control (BCCDC) reviewed its database on cases of LGV that were diagnosed in that province between November 2004 and

produced by



Canada's source for  
HIV and hepatitis C  
information

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October 2022. The researchers found a total of 545 cases distributed across the following periods:

- 2004 to 2017 – 205 cases (38%)
- 2018 to 2022 – 340 cases (62%)

The vast majority of cases (97%) were among gbMSM.

As the latter period of the study (2018 to 2022) is more relevant to the situation today, this article will focus on that.

### The era of HIV pre-exposure prophylaxis

In British Columbia, pre-exposure prophylaxis (PrEP) became widely available in 2018. Most cases of LGV (62%) occurred in the period from 2018 to 2022 and were among HIV-negative men who used PrEP. The researchers stated that cases of LGV in the PrEP era were “often” symptom free compared to the time before PrEP was widely available. Specifically, the distribution of symptom-free cases of LGV was as follows:

- PrEP users – 47%
- HIV-positive people – 33%
- HIV-negative not using PrEP – 29%

Among people with HIV, those with a history of syphilis were at heightened risk for LGV.

### Trends

The B.C. researchers found that cases of symptom-free LGV “increased considerably,” particularly among PrEP users (in the second period of the study). Among people with HIV, the proportion diagnosed with LGV decreased over the course of the study.

Overall, rates of LGV are increasing in B.C. This rise occurred around the same period that PrEP became available.

### Why did some changes with LGV occur?

Beginning in 2003, LGV infections in high-income countries like Canada were concentrated among HIV-positive people (mostly gbMSM). The B.C. researchers suggest that the availability of PrEP may be increasing the mixing of sexual partnerships between people who are HIV negative and people

who are HIV positive. The researchers also suggest that this mixing may in part be responsible for a shift in the populations affected by LGV.

The researchers noted that people who use PrEP undergo frequent screening (usually every three months) for STIs. It is therefore possible that increased screening for STIs in the PrEP era is detecting LGV relatively early in the course of infection, before symptoms have occurred. However, the researchers are not certain about this. Their findings underscore the need for further studies so that LGV in the current era can be better understood, not just in B.C. but in the rest of Canada.

### In Western Europe

Studies in Belgium and France have also found an increased rate of LGV among gbMSM who use PrEP. In many cases reported, LGV was also symptom free.

Four of the largest HIV and STI clinics in Austria recently pooled their data on LGV for analysis. Data were collected from April 2014 to November 2020 in the cities of Vienna, Innsbruck, Linz and Graz. Researchers found that nearly half of the cases of LGV were symptom free. Most cases of LGV occurred in men with HIV (64%) compared to men without HIV (46%).

One reason for the lower rates of LGV in HIV-negative men in the Austrian study is that researchers there noted that the cost of PrEP is not fully subsidized and not as widely used as it is in other places.

### Bear in mind

Recent reports from Austria, Belgium and British Columbia indicate that LGV is increasingly found in gbMSM. In many cases, LGV infection is symptom free. However, this may be due to the infection being found early. In all three places, more cases of LGV are being diagnosed in gbMSM who use PrEP.

Taken together, the data from B.C. and elsewhere underscore the need for frequent screening for STIs (including LGV) among gbMSM, including PrEP users. The data also draw attention to the need for more research on LGV in high-income countries.

## Resources

Lymphogranuloma Venereum – *Government of Canada*

Chlamydia and LGV guide: Key information and resources – *Government of Canada*

## REFERENCES:

Gupta AK, Lyons B, Hunter I, et al. The resurgence of lymphogranuloma venereum (LGV): changing presentation of LGV in the era of HIV pre-exposure prophylaxis (PrEP), 2004-2022. *Sexually Transmitted Diseases*. 2024; *in press*.

Chromy D, Sadoghi B, Gasslitter I, et al. Asymptomatic lymphogranuloma venereum is commonly found among men who have sex with men in Austria. *Journal der Deutschen Dermatologischen Gesellschaft*. 2024; *in press*.

## B. Exploring erectile dysfunction in gay, bisexual and other men who have sex with men

Thanks to the tremendous power of HIV treatment (antiretroviral therapy; ART), many people taking it will live well into their senior years. As the risk of life-threatening infections related to AIDS decreases for people who successfully use ART, other conditions become more of a concern. One such issue is erectile dysfunction (ED).

A team of researchers in the U.S. and at the University of Toronto analysed data from 625 gay, bisexual and other men who have sex with men (gbMSM), some of whom had HIV. Researchers were able to home in on risk factors for ED. They also were able to formulate recommendations for clinicians caring for gbMSM to help minimize the risk of ED in their patients.

### Study details

Researchers analysed health-related information from 625 men who were part of a larger ongoing study in the U.S. called MACS (Multicenter AIDS Cohort Study). Participants were recruited from Baltimore, Los Angeles, Pittsburg and Washington, DC.

The average profile of the men at the time data were collected was as follows:

- age – 62 years
- HIV positive – 285 men (46%)
- HIV negative – 340 men (54%)
- main ethno-racial groups: White – 61%; Black – 26%; Hispanic – 13%
- 58% had high blood pressure
- 14% had diabetes
- 95% were taking ART and had a suppressed viral load

Information about ED was captured on questionnaires that the men periodically answered.

## Results

Statistical analysis found that men with HIV were 41% more likely to have ED than men without HIV.

Among HIV-positive men, factors that were linked to an increased risk for ED were as follows:

- older age
- being Hispanic (explained later)
- having diabetes
- using antidepressants

Among men without HIV, risk factors for ED were as follows:

- tobacco smoking (the more years they smoked, the greater the risk)
- older age

## A closer look at some risk factors

### Age

Some aging-related factors contribute to an increased risk for ED. One such factor is the gradual decline in testosterone levels. An increased risk for ED also may be connected to the gradual loss of cells in the penis that play a role in maintaining erections.

### Diabetes and cardiovascular disease

Diabetes and cardiovascular disease are associated with changes to blood vessels that make them less flexible and reduce blood flow.

### Mental health

Depression and anxiety can increase the risk of ED. Sometimes antidepressants can improve ED; however, in some cases antidepressants can also worsen ED.

### Smoking

Smoking affects the health of arteries and reduces the flow of blood to organs and the penis.

### A note about ethnicity in this study

The present study found a statistical link between being Hispanic and an increased risk of ED. However, the proportion of Hispanic men in the study was low and the link with ED may not be clinically meaningful because Hispanic men in the study may have had a cluster of underlying factors that increased their overall risk for ED. The apparent statistical link between ethnicity and ED may have occurred for reasons that had nothing to do with ethnicity.

### What to do

The researchers encouraged healthcare providers to screen their gbMSM patients (regardless of HIV status) for ED. In addition, they encouraged screening for factors linked to ED, such as diabetes, cardiovascular disease, cigarette smoking and so on. This screening could uncover ED and its drivers and could allow clinicians to provide advice tailored to each patient so that these issues can be dealt with.

The researchers also recommended that healthcare providers screen gbMSM for depression and refer patients to receive counselling for help with mood-related issues. They encouraged doctors to prescribe “the lowest effective dose” of antidepressants. When ED appears to be caused by an antidepressant, the researchers encouraged doctors to switch to another class of antidepressant to reduce the risk of ED.

### General risk factors for ED

According to the Mayo Clinic, the following general factors, some of which were found in the MACS study, can increase the risk for ED:

- medical conditions, particularly diabetes or heart conditions

- tobacco use
- being overweight
- certain medical treatments, such as prostate surgery or radiation treatment for cancer
- injuries, particularly if they damage the nerves or arteries that control erections
- medications, including antidepressants, antihistamines and treatment for high blood pressure, pain or prostate conditions
- psychological conditions, such as stress, anxiety or depression
- drug and alcohol use, especially if you’re a long-term drug user or heavy drinker

These issues should be discussed with a doctor or nurse and advice sought for dealing with them.

### Resource

Erectile Dysfunction Guidelines — *Canadian Urological Association*

### REFERENCES:

Mustapha A, Polanka BM, Maini M, et al. Incidence of erectile dysfunction among middle-aged and aging sexual minority men living with or without HIV. *Frontiers in Public Health*. 2024 Jan 24; 12:1302024.

Guimaraes EL, Dias DO, Hau WF, et al. Corpora cavernosa fibroblasts mediate penile erection. *Science*. 2024; *in press*.

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## II HIV

### A. Trends in causes of death in people with HIV across 24 years

When used as directed, HIV treatment (antiretroviral therapy; ART) is highly effective. Researchers increasingly expect that many ART users will have near-normal life expectancy.

To better understand factors that can reduce life expectancy in people with HIV who use ART, a team of researchers in North America and Western Europe pooled their data collected between 1996 and 2020.

Among nearly 190,000 people studied, nearly 9% died. Over the course of the 24-year study, the overall risk of death decreased for most participants. Initially, the most common cause of death was

from complications related to AIDS. However, such deaths fell markedly over the course of the study, and deaths from heart disease and cancers (unrelated to HIV or liver issues) increased.

Troublingly, deaths from complications related to drug use rose among participants from North America. Women who injected drugs were at heightened risk for dying compared to men who injected drugs.

The researchers recommended interventions to improve the health of people with HIV so that the benefits of ART can be experienced more equitably across different populations.

### Study details

Researchers analysed data from 189,301 people with HIV. All participants entered the study when they began to use ART and their average profile at that time was as follows:

- 77% men, 23% women
- 37 years old
- 19% had AIDS
- 8% tested positive for antibodies to hepatitis C virus (HCV), indicating that they had been exposed to it

### Results

Over the course of the study, 16,832 people (9%) died.

The most common causes of death were as follows:

- AIDS-related complications – 25%
- cancer unrelated to AIDS or hepatitis – 14%
- heart disease – 8%

Note that data on the cause of death among 22% of participants was missing.

### Trends in time

During the study, deaths from AIDS-related causes fell from nearly 50% in the period from 1996 to 1999 to 19% in the period from 2016 to 2020.

For certain populations—gay, bisexual and other men who have sex with men (gbMSM),

heterosexual men and women who acquired HIV via sexual contact—the risk of death fell markedly.

Among men who acquired HIV via sharing equipment for drug use, the risk of death fell modestly.

Among women who injected drugs, the risk of death *increased* over time. Lung infections as a cause of death in these women increased over time.

People who were co-infected with HCV had a smaller decline in their risk of death than people who were not co-infected with this virus.

### The importance of high CD4+ cell counts

In general, researchers found that people who had high CD4+ cell counts (from using ART) were less likely to die than people with lower CD4+ cell counts.

### North America vs. Europe

Declines in the risk of death were generally greater for people living in North America than in Western Europe. An exception to this trend was as follows: People from North America who used drugs had an increased risk of death over time compared to people from Western Europe who used drugs. Researchers suggested that the reasons for this difference in the risk of death were as follows:

- increased rates of opioid use in North America
- increased risk of drug poisoning in North America
- greater use of opioid substitution therapies (buprenorphine and methadone) in Western Europe

The researchers lacked access to important socioeconomic data such as the following:

- levels of education
- income
- housing status

Such factors could have affected the survival of participants.

## Women’s lives and what is needed

Carole Seguin-Devaux, PhD, a scientist at the Luxembourg Institute of Health, reviewed the study’s findings and commented in the journal *Lancet HIV* that “women who inject drugs are at increased risk of HIV because they face barriers in accessing harm reduction services and endure higher levels of stigma, discrimination, incarceration and gender-based violence than men.”

She encouraged health authorities to fund “evidenced-based harm reduction programmes” to help people who use drugs.

### REFERENCES:

Trickey A, McGinnis K, Gill MJ, et al. Longitudinal trends in causes of death among adults with HIV on antiretroviral therapy in Europe and North America from 1996 to 2020: a collaboration of cohort studies. *Lancet HIV*. 2024 Jan 24; S2352-3018(23)00272-2.

Seguin-Devaux C. HIV and people who inject drugs: inequality until death. *Lancet HIV*. 2024 Jan 24; S2352-3018(23)00295-3.

Krentz HB, Lang R, McMillan J, et al. The changing landscape of both causes and locations of death in a regional HIV population 2010-2021. *HIV Medicine*. 2024; *in press*.

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## III CANCER

### A. Prostate cancer in men with HIV

As people with HIV are living longer thanks to treatment (antiretroviral therapy; ART), they become at risk for issues related to aging.

Rates of prostate cancer in the U.S. are relatively high among men without HIV. Researchers at George Washington University in Washington, DC, reviewed medical records from their university’s cancer clinic. The researchers focused on cases of prostate cancer in men with HIV. They limited their review to cancers that were restricted to the prostate (in other words, the cancer had not spread from the prostate to other organs).

Their review, which encompassed the period from 2007 to 2020, found records of 79 patients with HIV who were diagnosed with prostate cancer.

The average profile of HIV-positive participants at the time they were diagnosed with prostate cancer was as follows:

- age – 61 years (ranging from 49 to 79 years)
- main ethno-racial groups: Black – 82%; White – 18%
- 34% had a close male relative with prostate cancer
- cancer grade: 17% had low-grade cancer; 44% had medium-grade cancer; 33% had high-grade cancer
- 92% were taking ART and 53% had an undetectable viral load
- CD4+ count – 436 cells/mm<sup>3</sup>

Participants were monitored for up to five years.

### Prostate cancer treatment

Common approaches to prostate cancer treatment included removal of the prostate followed by the use of drugs that reduced production of testosterone. The use of such drugs is sometimes necessary, as prostate cancer is sensitive to testosterone and depriving this cancer of testosterone helps to inhibit its growth. Patients with low-grade prostate cancer were frequently monitored and surgery and/or other treatment was offered if the cancer became more aggressive. Participants who had high-grade prostate cancer were treated with either radiation therapy and drugs that reduced testosterone production or removal of the prostate followed by radiation therapy to kill any residual cancer cells.

### Results

Overall, 98% of participants were alive five years after their diagnosis of prostate cancer. No one died from complications related to prostate cancer. One man died 11 years after his prostate cancer diagnosis from a severe bacterial infection arising from an inflamed intestine.

### CD4+ cell count changes

Some research centres reported a temporary decrease in CD4+ cell counts, particularly after radiation therapy for prostate cancer. For many patients with HIV, a lower CD4+ count can be psychologically distressing. However, the decreases in CD4+ cells were usually temporary and there

were no reports of increased risk of infections arising because of this.

In the present study, there was a trend to lowered CD4+ counts, usually a decrease of 150 cells/mm<sup>3</sup>. However, medical records were incomplete and not everyone's CD4+ count was available for analysis. Also, CD4+ counts were not available to the researchers after prostate cancer therapy cessation, so they could not be certain how long the decrease in CD4+ cells lasted.

### Effect of HIV

As HIV weakens the immune system, there is always concern that cancers may be more aggressive or less responsive to therapy in people with HIV. However, researchers found that HIV did not appear to cause a more aggressive course of prostate cancer. Certainly, the death rate in the men with HIV in the study was very low and no one died from prostate cancer. Ideally, the researchers should have had a group of HIV-negative men of the same age with prostate cancer for purposes of comparison.

### For the future

The present study is small and looked back upon data captured in the past; such studies are not suited to provide definitive results. However, hopefully the study will encourage other researchers to design prospective clinical trials to better understand prostate cancer in a larger number of men with HIV.

### Resource

Prostate Cancer Canada

### REFERENCE:

Vaziri T, Rao YJ, Whalen M, et al. Management of localized prostate cancer in men with human immunodeficiency virus: Analysis of a large retrospective cohort. *Clinical Genitourinary Cancer*. 2023 Oct;21(5):614.e1-614.e8.

## IV PANDEMICS

### A. Large UK study compares COVID-19 deaths in different populations with weakened immunity

The virus SARS-CoV-2 causes a disease called COVID-19. A pandemic caused by this virus began in 2020. Initially there was much fear about this virus because it was new, little was known about it and there were high rates of death among many hospitalized patients. Eventually vaccines were developed that greatly reduce the risk for serious illness, hospitalization and death.

Although SARS-CoV-2 continues to mutate, boosters have been developed and are regularly modified to keep pace with major mutations developed by the virus.

One main concern about SARS-CoV-2 was its impact on different populations, particularly people with weakened immune systems.

A team of researchers at Oxford University and the UK Health Security Agency scoured the scientific literature for studies published between 2020 and 2022. They focused on the risk of death in people diagnosed with COVID-19.

The review encompassed 99 studies with data from adults in the following populations:

- 1,542,097 people who had a weakened immune system
- 56,248,181 people who did not have a weakened immune system

Among immune-suppressed people, researchers focused on the following subpopulations:

- recipients of transplanted organs (specifically liver, kidney, lung and heart)
- people with cancer; subdivided into people with blood cancers and people with solid tumours
- HIV infection
- inflammatory diseases of the bone and joints
- inflammatory diseases of the skin (such as psoriasis)
- inflammatory diseases of the gut (such as Crohn's disease and colitis)

Researchers divided people as follows:

- by age group
- by whether they lived in high-, medium- or low-income countries
- by whether they were hospitalized
- by the year that they were in a study (2020, 2021 and 2022)

Most of the studies reviewed came from high-income countries.

## Results

People who received organ transplants or who had cancer (and whose cancers were untreated) were more likely to die from complications of COVID-19.

People whose cancers were being treated or people who had HIV or arthritis were less likely to die from COVID-19-related complications.

Note that researchers were not able to subdivide people with HIV by CD4+ cell count, use of HIV treatment (antiretroviral therapy; ART), type of ART used, viral load or underlying risk factors (such as heart disease, diabetes, high blood pressure, obesity and so on).

As with multiple other studies, researchers found that younger people were less likely to die than older people.

The overall findings from the present study are in broad alignment with several other major studies.

## Bear in mind

The present study's analysis should be seen as an overview. Every person has their own individual risk factors depending on their overall health. For people with HIV in particular, factors such as CD4+ cell count and viral suppression are important; however, these were missing from the study's analysis. The study is useful as a crude tool for an overview of different populations. However, it cannot be used to derive individual health management strategies for people with HIV concerning their risk of dying from COVID-19.

The study did not assess whether populations had different intensities of COVID-19 or risks for long COVID. Other research teams are in the process of

analyzing data from different sub-groups of people with HIV and their risk for COVID-19.

## Note well

As mentioned earlier, for people with HIV, overall health, CD4+ cell count and viral load are all important factors to consider when discussing COVID-19-related issues with their healthcare provider.

A crucial step to better health for people with HIV is initiating ART and achieving and maintaining a suppressed viral load. It is important to discuss with healthcare providers possible causes of persistently detectable viral loads, if this is an issue.

A second step to better health is discussion of booster shots to reduce the risk of COVID-19-related complications (severe illness, hospitalization and death). The virus that causes COVID-19 is constantly mutating, so having regular booster shots on a schedule advised by a physician is important.

Discussion with a healthcare provider about steps to take to reduce possible exposure to SARS-CoV-2 is also important. Depending on one's medical history and overall health, physicians may advise some patients to avoid crowded conditions and to wear a mask if this cannot be avoided.

In addition to regular boosters to reduce the risk for COVID-19, vaccinations against influenza, bacterial pneumonia and other respiratory conditions (such as respiratory syncytial virus, or RSV) can be useful.

## REFERENCE:

Leston M, Elson W, Ordóñez-Mena JM, et al. Disparities in COVID-19 mortality amongst the immunosuppressed: A systematic review and meta-analysis for enhanced disease surveillance. *Journal of Infection*. 2024 Jan 30;88(3):106110.

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## B. Focusing on serotonin and other approaches to long COVID

The virus SARS-CoV-2 causes a disease called COVID-19. Most people who develop acute COVID-19 recover. However, some people who recover from acute COVID-19 subsequently develop lingering symptoms commonly called long COVID.



Symptoms associated with long COVID can include the following (this list is not exhaustive):

- persistent and disabling fatigue
- loss of endurance
- difficulty breathing
- headache
- problems with sleep
- difficulty concentrating
- memory problems
- difficulty thinking clearly

Part of the difficulty of finding a treatment for long COVID is that researchers are uncertain why it occurs, why some people get it and others do not, and why it lasts for a few weeks or months in some people or even longer in others.

A team of researchers, including leading immunologists and infectious disease specialists, has been studying more than 1,500 people who developed COVID-19, some of whom subsequently developed long COVID.

The researchers undertook extensive analysis of tissues and samples from patients to understand what had happened to them. They also conducted experiments with laboratory animals to better understand the mechanisms that viruses can use to cause chronic problems. The researchers' findings led them to explore serotonin.

### About serotonin

Serotonin is a messenger molecule that is used to send signals from one cell to another. There are receptors for serotonin on nearly every major organ system in the body, including the following:

- cardiovascular system
- gastrointestinal system
- lungs
- genitourinary system
- nervous system

Serotonin and its receptors help to regulate energy, digestion, appetite and production of some hormones. They also affect mood, memory and libido.

Emerging research suggests that serotonin may play a role in regulating aspects of immunity.

### Key findings

SARS-CoV-2 infection or fragments of the virus can persist at very low levels in the intestinal tract of some people with long COVID. This residual virus or fragments of the virus can incite inflammation and the production of interferon. These factors (residual virus, inflammation and interferon production) appear to reduce the absorption of the precursor used to make serotonin—an amino acid called tryptophan. This amino acid is also used to make melatonin, and reduced tryptophan could lead to reduced melatonin levels, which could affect sleep. Participants in the present study who had severe symptoms of long COVID had diminished serotonin levels.

Most of the body's serotonin is made in the gastrointestinal tract. Serotonin is then stored in platelets, cells that are plentiful in the blood and help regulate blood clotting. Micro-clots form in both people with acute COVID and long COVID. As platelets may have insufficient serotonin caused by SARS-CoV-2 infection (and the resulting inflammation this virus causes), they may not be able to fully regulate the formation of blood clots, leading to excessive formation of micro-clots. Such clots could decrease the flow of blood to vital organs, degrading their function and in some cases, cause serious symptoms.

The vagus nerve sends signals from the brain to the heart, lungs and digestive tract (and vice versa). This nerve is involved in some of the automatic functions in the body, such as breathing, heart rate and so on. The researchers think that the inflammation in the gut and body caused by SARS-CoV-2 sends signals to the brain via the vagus nerve when serotonin levels in the gut and other places are low. These signals to the brain likely incite inflammation within this vital organ. Inflammation in the brain may play a role in chronic fatigue, sleeping problems, anxiety/depression and memory loss—all of which have been reported in people suffering from long COVID.

Further studies are needed to confirm the connection between reduced serotonin levels and long COVID found in the present study.

Experiments in animals suggest that focusing on serotonin may be a potential route to helping people with long COVID. Large randomized clinical trials are needed to safely assess the impact of drugs that affect serotonin—such as selective

serotonin reuptake inhibitors (SSRIs) or precursors of serotonin (such as 5-hydroxytryptamine, or 5HTP)—in people with long COVID.

### Noteworthy

Many of the mechanisms that could affect serotonin levels found in the present study can occur in other viral infections (such as dengue virus infection, which can cause long-term issues) and in non-viral infections such as multiple sclerosis and lupus.

### Exploring low-dose naltrexone

A team of researchers in Dublin, Ireland, tried a different approach to long COVID. The researchers used low doses of the drug naltrexone—a treatment that can help some people overcome dependency on alcohol and opioids. At high doses (50 mg), naltrexone affects opioid receptors. However, a lower dose (between 1 to 4.5 mg/day) may have different and complex effects, such as reducing inflammation within the immune system and altering the behaviour of cells of the immune system. Some immune system cells patrol the brain to control infections in that organ. Low-dose naltrexone is thought to help these cells release signals that dampen inflammation in the brain.

The study from Ireland, which was small and uncontrolled, suggests that low-dose naltrexone may be useful in some people with long COVID. Other small and uncontrolled studies from the U.S. have also found similar promising results. However, large randomized clinical trials will be needed to confirm the effects of low-dose naltrexone in this population.

### Another approach

An increasing number of studies suggest that repeated booster shots of COVID-19 vaccines could have a beneficial effect in reducing the risk for long COVID.

### Long COVID and the brain

Headache, sleeping problems and cognitive issues (commonly called “brain fog”) are common in people who have long COVID. Another team of scientists in Dublin, Ireland, has found that some of the blood vessels in the brains of people with long COVID are “leaky.” The excess inflammation caused

by COVID-19 may have an adverse impact on the health and integrity of blood vessels in the brain. In turn, this may play a role in the development of brain symptoms of long COVID-19.

This team of scientists needs to find ways to both prevent and treat the formation of leaky blood vessels to assess if such interventions can improve the health of people with long COVID.

### REFERENCES:

Berger M, Gray JA, Roth BL. The expanded biology of serotonin. *Annual Review of Medicine*. 2009; 60:355-66.

Zhang Y, Bharathi V, Dokoshi T, et al. Viral afterlife: SARS-CoV-2 as a reservoir of immunomimetic peptides that reassemble into proinflammatory supramolecular complexes. *Proceedings of the National Academy of Sciences USA*. 2024 Feb 6;121(6): e2300644120.

Wong AC, Devason AS, Umana IC, et al. Serotonin reduction in post-acute sequelae of viral infection. *Cell*. 2023 Oct 26; 186(22):4851-4867.e20.

O’Kelly B, Vidal L, McHugh T, et al. Safety and efficacy of low-dose naltrexone in a long COVID cohort: an interventional pre-post study. *Brain, Behavior and Immunity—Health*. 2022 Oct; 24:100485.

Isman A, Nyquist A, Strecker B, et al. Low-dose naltrexone and NAD+ for the treatment of patients with persistent fatigue symptoms after COVID-19. *Brain, Behavior and Immunity—Health*. 2024 Feb 1; 36:100733.

Greene C, Connolly R, Brennan D, et al. Blood-brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment. *Nature Neuroscience*. 2024; *in press*.

MacCallum-Bridges C, Hirschtick JL, Patel A, et al. The impact of COVID-19 vaccination prior to SARS-CoV-2 infection on prevalence of long COVID among a population-based probability sample of Michiganders, 2020-2022. *Annals of Epidemiology*. 2024; *in press*.

Maier HE, Kowalski-Dobson T, Eckard A, et al. Reduction in long COVID symptoms and symptom severity in vaccinated compared to unvaccinated adults. *Open Forum Infectious Diseases*. 2024 Jan 23;11(2): ofae039.

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## C. Canadian researchers study COVID-19 vaccine effectiveness in people who use drugs

SARS-CoV-2 is the virus that causes an illness called COVID-19. Vaccines and booster shots that greatly reduce the risk of COVID-19-related complications, including serious illness, hospitalization and death, are available. Boosters are updated from time to time to enhance protection from variants of SARS-CoV-2, as the virus is constantly mutating.

## Canadian research

A team of Canadian researchers conducted a large study to estimate the effect of COVID-19 vaccination in different populations, including people with a history of injecting drugs.

The researchers analysed health-related information from databases in British Columbia. The information they accessed had been rendered anonymous so that individuals could not be identified. The data were collected between December 2020 and November 2021. Participants had all been tested for SARS-CoV-2 infection and the whole study population was distributed as follows:

- 2,700 people with HIV
- 375,043 people without HIV

Researchers divided the study population into four groups:

- people with HIV who injected drugs
- people with HIV who did not inject drugs
- people without HIV who injected drugs
- people without HIV who did not inject drugs

## Results

In general, the researchers' findings suggested that people with HIV who use drugs may have reduced vaccine effectiveness against the risk of developing COVID-19. A similar finding occurred among people without HIV who used drugs.

Citing their previous studies, the researchers stated that a combination of “substance use and/or comorbidities that occur in [people who inject drugs]” may partially weaken the immune system, which would explain the findings in the present study.

There also may have been unmeasured issues that could have adversely affected the health of people who injected drugs, such as living in close quarters or crowded conditions or having difficulty maintaining physical distancing from other people (to reduce the risk of infection from SARS-CoV-2).

The researchers hope to conduct future analyses and refine their findings.

## Help for people who inject drugs

The researchers suggested that that people who inject drugs should be prioritized for receiving booster doses of COVID-19 vaccines.

They noted that people who inject drugs face stigma and discrimination and can develop mistrust of the medical system. Therefore, interventions to reach people who inject drugs will require strategies to overcome these barriers.

## REFERENCE:

Puyat JH, Wilton J, Fowokan A, et al. COVID-19 vaccine effectiveness by HIV status and history of injection drug use: a test-negative analysis. *Journal of the International AIDS Society*. 2023 Oct;26(10):e26178.

## D. Barcelona researchers find an increased risk for cardiovascular problems after recovery from COVID

The virus SARS-CoV-2 causes an illness called COVID-19. Vaccines and booster doses that greatly reduce the risk of COVID-19-related complications, including serious illness, hospitalization and death, are available.

Studies done in people without HIV have found that after recovery from acute COVID-19 some people become at heightened risk for cardiovascular events such as heart attack and stroke.

A team of researchers in Barcelona, Spain, collected and analysed health-related information from adults with HIV, some of whom developed COVID-19. Researchers had access to detailed medical information from participants, including the following:

- results of testing for SARS-CoV-2
- reasons for any hospitalizations
- COVID-19 vaccination
- presence of comorbidities (including cardiovascular disease)
- CD4+ cell counts in people with HIV

Researchers were particularly interested in the length of time after an episode of acute COVID-19 that it took participants to experience what they

called a “cardiovascular event,” which they defined as one or more of the following:

- heart attack
- stroke
- abnormal heart rhythm
- heart failure
- inflammatory heart disease (myocarditis, pericarditis)
- injury or blockage of blood vessels away from the heart such as closer to the limbs (peripheral vascular disease)
- excessive clotting of blood, leading to reduced flow of blood to organs/tissues
- other cardiac disorders

Researchers focused on the years 2020 to 2022.

In the study, there were 4,199 people with HIV and 14,004 people without HIV. The average age of the whole study population was 47 years; 82% were men and 18% were women.

## Results

Cardiovascular events that occurred during the study were distributed as follows:

- people with HIV who developed COVID-19 – 5% had a cardiovascular event
- people with HIV who did not get COVID-19 – 4% had a cardiovascular event

The most common cardiovascular events were as follows:

- heart attack
- heart failure
- stroke

People with HIV who developed COVID-19 were twice as likely to get excess blood clots, which affected the flow of blood, and heart failure than people with HIV who did not develop COVID-19.

Even when researchers reanalyzed the data and excluded people with any previous diagnoses of cardiovascular disease, people with HIV were still at heightened risk for cardiovascular problems after recovering from acute COVID-19 (compared to people who were not diagnosed with COVID-19).

People who were hospitalized because of COVID-19 were more likely to have subsequent cardiovascular

events in a shorter timespan compared to people who had never been hospitalized for COVID-19.

## Risk factors

The researchers found that the following factors were associated with an increased risk for cardiovascular events after a person had been diagnosed with COVID-19:

- age 40 or older
- heterosexual men (vs. gay and bisexual men)
- having chronic liver or kidney disease
- having a history of previous cardiovascular events
- having cancer

## Bear in mind

Researchers found that, overall, people with HIV who had been diagnosed with COVID-19 had a 30% increased risk for cardiovascular events compared to people with HIV who did not get diagnosed with COVID-19.

This risk was greatest for the first six months after acute COVID-19 but persisted at a lower level for up to 12 months after acute COVID-19 had occurred.

Even people with HIV who were not at heightened risk for cardiovascular disease became at risk for cardiovascular events after they developed COVID-19.

## In context

The results from the Barcelona study should not be surprising. Studies from Denmark, Sweden and the U.S. in people without HIV found that there was a significantly increased risk of cardiovascular events up to a year after acute COVID-19, whether or not people had been hospitalized for COVID-19.

## Ideas for care

The Barcelona researchers recommended that clinicians consider the increased risk for cardiovascular events (found in the present study) that can occur in people with HIV after they have recovered from acute COVID-19, “regardless of COVID-19 severity or the presence of [preexisting] cardiovascular disease.”

The researchers stated that their study underscores the importance of COVID-19 vaccination and booster doses for people with HIV and other populations at risk for cardiovascular disease.

The researchers recommended “assessing and managing cardiovascular disease risk among people with HIV recovering from COVID-19 and initiating timely [cardiovascular disease] prevention and treatment options for these individuals.”

#### REFERENCE:

Martín-Iguacel R, Moreno-Fornés S, Bruguera A, et al. Major cardiovascular events after COVID-19 in people with HIV. *Clinical Microbiology and Infection*. 2024; *in press*.

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