



Frequently Asked Questions on Antiviral Therapy for Adults with Mild to Moderate COVID-19

Date: April 2, 2024

This document was developed by Ontario Health’s Infectious Diseases Advisory Committee (IDAC) based on best available evidence and expert consensus. There are limitations to the evidence that is currently available. **Prescribers should conduct a comprehensive risk-benefit analysis when applying the recommendations to inform individualized treatment decisions.**

Introduction

This document is intended to provide additional information as a supplement to the [Ontario Health Recommendations for Antiviral Therapy for Adults with Mild to Moderate coronavirus disease 2019 \(COVID-19\)](#). Due to the evolving COVID-19 pandemic, this guidance document will be updated as new relevant information becomes available.

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1. Pregnancy

Preamble: Antiviral use in pregnant patients with COVID-19

The Committee recommends using an individualized and informed, shared decision-making approach by a multidisciplinary team with suitable expertise in the management of pregnancy to assess the risks and benefits of antiviral use in pregnant patients with COVID-19.

This risk-benefit assessment may include medical comorbidities, pre-pregnancy body mass index, vaccination history and other risk factors the patient may have for severe COVID-19.¹ Compared with pregnant people without COVID-19, people who are pregnant with symptomatic COVID-19 infection are at increased risk for severe disease or pregnancy-associated complications such as hospitalization, admission to an intensive care unit, need for mechanical ventilation, preeclampsia, eclampsia, maternal death, caesarean delivery, preterm birth, stillbirth and thromboembolic disease.^{2,3}

In addition to the FAQs below, more information on COVID-19 and pregnancy can be found under [Additional Resources](#).

1A. Can nirmatrelvir/ritonavir be used in pregnant people?

Ritonavir has been used extensively during pregnancy in people with HIV and has a favourable safety profile during pregnancy.^{1,4} Although there are no randomized controlled trials of combination nirmatrelvir and ritonavir use in pregnant and lactating people, the mechanisms of action for nirmatrelvir and ritonavir, along with the results of case series and animal studies suggest that this regimen can be safely used in pregnant individuals.^{1,4,5} Health care providers should ensure the patient has no contraindications and review any possible drug-drug interactions, including how to manage them before prescribing nirmatrelvir/ritonavir.³

Observational studies found nirmatrelvir/ritonavir to be well-tolerated and not associated with an increase in serious adverse effects in pregnant patients or their baby.⁶⁻⁸ During the Omicron era, a retrospective study of 6,250 symptomatic pregnant patients reported nirmatrelvir/ritonavir treatment was associated with a reduced risk of a maternal morbidity and *mortality* index (MMMI) event within 28 days of starting treatment.⁹ A MMMI event is defined as having at least one of the following pregnancy-related morbidities: vaginal bleeding, pregnancy-induced hypertension, preeclampsia, eclampsia, haemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, preterm birth, infection requiring antibiotics or maternal death, admission to ICU or referral for higher dependency care.⁹ The data from observational studies are mixed for whether nirmatrelvir/ritonavir treatment is associated with a reduced risk of preterm delivery or caesarean section in pregnant patients with COVID-19.^{7,9}

1B. Can remdesivir be used in pregnant people?

Remdesivir can be used in pregnant patients with COVID-19.¹

Limited data from observational studies suggest that remdesivir is well-tolerated in the second and third trimesters with a low risk of serious adverse events.^{1,10} There is a paucity of data for remdesivir use in the first trimester.¹⁰ An observational study of 95 pregnant patients with moderate, severe or critical COVID-19 reported similar maternal and neonatal outcomes in the 39 patients who received remdesivir compared to those who had not.^{1,11} The data from observational studies are mixed on whether remdesivir use is associated with an increase or decrease in preterm delivery or caesarean section.^{12,13} Elevated transaminases have been commonly reported in observational studies and post-marketing surveillance databases, but grade 3 (severe or medically significant) abnormalities were uncommon.^{1,11,14}



2. Breastfeeding or Chestfeeding

Preamble: Antiviral use in patients with COVID-19 and breastfeeding or chestfeeding

The Committee recommends that the decision to breastfeed/chestfeed during COVID-19 antiviral therapy be a shared decision between the patient and clinical team. When possible, breastfeeding/chestfeeding should continue while taking hygiene precautions due to its nutritional benefits and the protection it may confer to the infant from antibodies and other immunological factors.¹⁵

Current evidence suggests that breast milk is not a source of COVID-19 infection.³ However, individuals with suspected or confirmed COVID-19 can transmit the virus through respiratory droplets while in close contact with the infant, including while breastfeeding/chestfeeding.³ Other factors to consider include the benefits of breastfeeding/chestfeeding, the postnatal age of the infant, the need for the medication, any underlying risks of exposing the infant to the drug, and the potential adverse outcomes of COVID-19.¹

For patients with suspected or confirmed COVID-19 who intend to infant feed with breast milk, the Committee recommends that obstetricians/gynecologists and other parental care practitioners provide counselling on how to minimize the risk of transmission. These measures may include hand hygiene, wearing a medical face mask while breastfeeding/chestfeeding, breast milk expression using a dedicated manual or electric breast pump, proper pump cleaning after each use or having someone who does not have suspected or confirmed COVID-19 infection and is not sick feed the expressed breast milk.³

In addition to the FAQs below, more information on COVID-19 and breastfeeding/chestfeeding can be found under [Additional Resources](#).

2A. Can nirmatrelvir/ritonavir be used in patients who are breastfeeding or chestfeeding?

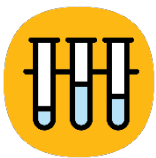
Breastfeeding/chestfeeding can continue while a patient receives nirmatrelvir/ritonavir.¹

There are extensive data on the safety of ritonavir as part of antiretroviral therapy in pregnant people with HIV.¹ Although ritonavir passes into breast milk, the low levels of the drug that have been measured in the blood of some breastfed infants is not considered to be clinically significant.^{1,16} There have not been any reports of adverse reactions to ritonavir in breastfed infants.¹⁶ Nirmatrelvir has poor oral absorption and the levels absorbed from breast milk ingestion are unlikely to be clinically relevant or expected to cause adverse effects in an infant.^{1,17}

2B. Can remdesivir be used in patients who are breastfeeding or chestfeeding?

Breastfeeding/chestfeeding can continue while a patient receives remdesivir.¹

Remdesivir and its predominant active metabolite (GS-441524) are poorly absorbed from the gastrointestinal tract and infants are unlikely to absorb clinically important amounts from breast milk.^{14,18} One case report estimated the relative infant doses of remdesivir and GS-441524 in breast milk as 0.007% and 1.6%, respectively.¹⁸ No adverse effects have been documented in the small number of infants exposed to remdesivir and its metabolite via breast milk.^{14,18}



3. Renal and Hepatic Function Testing

Aspartate aminotransferase (AST) testing is NOT recommended as part of hepatic function assessment and monitoring. AST is non-specific to the liver compared to ALT and may be elevated in skeletal and cardiac muscle, red blood cells, kidneys and brain disorders.^{19,20}

3A. Is renal and/or hepatic function testing required for the initiation of nirmatrelvir/ritonavir or during therapy in the outpatient setting?

The Committee does not recommend delaying nirmatrelvir/ritonavir initiation in patients without recent laboratory results given its 5-day window for initiation and relatively short duration if treatment benefits outweigh potential risks based on clinical judgment. The Committee acknowledges timely access to laboratory testing may be a challenge in some patients.

Nirmatrelvir/ritonavir requires dose adjustment in patients with moderate to severe renal impairment. For patients where underlying moderate to severe renal impairment is suspected, the latest available estimated glomerular filtration rate (eGFR) can be used to guide initial treatment and additional lab tests may be ordered at the discretion of the provider to adjust treatment.

Nirmatrelvir/ritonavir is not recommended for patients with known or suspected severe hepatic impairment (i.e., Child-Pugh Class C) due to a lack of pharmacokinetic and safety data.²¹ For patients without recent hepatic function testing results (e.g., bilirubin, INR, serum albumin) where severe impairment is suspected, the latest available bloodwork can be used to guide initial

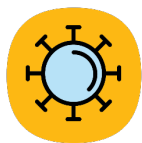
treatment and additional lab tests may be ordered at the discretion of the provider to adjust treatment.

3B. Is renal and/or hepatic function testing required for the initiation of remdesivir or during therapy in the outpatient setting?

The Committee does not recommend delaying remdesivir initiation in patients without recent laboratory results given its 7-day window for initiation and relatively short duration of therapy if treatment benefits outweigh potential risks based on clinical judgment. The Committee acknowledges timely access to laboratory testing may be a challenge in some patients.

The product monograph recommends assessment of a patient's eGFR, alanine transaminase (ALT) and prothrombin time (PT) prior to starting remdesivir and during treatment as clinically appropriate.²² It is not necessary to obtain a baseline eGFR in patients with renal impairment prior to remdesivir initiation, including those requiring dialysis, as renal-dose adjustments are no longer required.²² In clinical trials of non-hospitalized patients receiving of a 3-day course of remdesivir, a decrease in eGFR was not a commonly reported adverse effect.²³

The latest available ALT can be used to guide initial treatment. For patients where an elevated ALT is suspected or may be of concern (e.g., in patients with pre-existing liver impairment), it may be ordered at the discretion of the provider. ALT elevations during remdesivir therapy are common but are generally asymptomatic and fully reversible after discontinuation of therapy.²⁴ Remdesivir is not recommended in patients who develop equal to or greater than 5 times the upper limit of normal during treatment or if the ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase or INR.²² Although increased PT has been observed in some patients treated with remdesivir compared to placebo, no significant difference in bleeding incidents was found between the two groups.²²



4. COVID-19 Post-Exposure Prophylaxis

4A. Is nirmatrelvir/ritonavir recommended for post-exposure prophylaxis?

The Committee does not recommend the use of nirmatrelvir/ritonavir for COVID-19 post-exposure prophylaxis (PEP).

To date, the evidence for the use of nirmatrelvir/ritonavir for PEP has been negative. The unpublished EPIC-PEP trial evaluated a 5- or 10-day course of nirmatrelvir/ritonavir compared to a 10-day course of placebo in 2,954 household contacts of symptomatic COVID cases.^{25,26} The predominant circulating COVID-19 strain during the trial period was the Delta variant, although the Omicron variant was also observed in the latter part of the study.²⁵ Preliminary results did not report any significant difference for the primary efficacy endpoint of symptomatic COVID-19 development through day 14. The event rates were 2.6%, 2.4% and 3.9% in the nirmatrelvir/ritonavir 5-day group, 10-day group and placebo group, respectively.²⁵ For the secondary outcome of hospitalization or all-cause mortality through day 28, each treatment arm had one COVID-19-related hospitalization and no deaths.²⁵

Nirmatrelvir/ritonavir is not recommended for PEP given the lack of benefit observed in studies, combined with its known risk for adverse effects and drug interactions. Nirmatrelvir/ritonavir should be reserved for patients with symptomatic confirmed COVID-19.

4B. For patients with rebound COVID-19, is re-treatment or an extended duration of antiviral therapy recommended?

The Committee does not recommend re-treatment or an extended duration of antiviral therapy for COVID-19 rebound.

Rebound COVID-19 is defined as a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative.²⁷ The phenomenon has been observed in some patients who have completed treatment with nirmatrelvir/ritonavir or molnupiravir, and in patients in the absence of antiviral treatment.^{1,28} The reported rates of rebound COVID-19 range from less than 2% to up to 30% in clinical trials and observational studies.^{28–35}

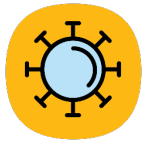
Rebound COVID-19 usually occurs within 2 to 8 days of completing a 5-day course of nirmatrelvir/ritonavir.^{1,28} The symptoms associated with rebound COVID-19 are typically mild and self-limiting.^{27,29,32} No hospitalizations or deaths have been reported in studies of outpatients who experienced rebound COVID-19.³⁶ To date, there have not been any reports of rebound COVID-19 following remdesivir therapy. The reason is unknown but the longer half-life of remdesivir's active metabolite compared to nirmatrelvir has been speculated as an explanation.^{1,27,30,37} The mechanism of COVID-19 rebound is not fully understood. Proposed mechanisms include the natural biphasic pattern of the viral life cycle that corresponds to the different stages of the patient's immune response and viral shedding, or the transient suppression of viral replication by antivirals without complete clearance followed by a resurgence of viral replication after the treatment course is complete.^{30,32,38} Rebound COVID-19 has not been found to be associated with reinfection or the development of resistance to nirmatrelvir/ritonavir.²⁷

There is currently no evidence for additional treatment with nirmatrelvir/ritonavir or other COVID-19 therapies in cases where COVID-19 rebound is suspected.^{1,27} Case reports have reported improvement or resolution of illness and positive COVID-19 test results without additional COVID-19 therapy.²⁷ The Committee recommends patient monitoring for symptomatic rebound COVID-19 and to follow the latest guidance from the [Ontario Ministry of Health on self-isolation and precautions](#) to prevent COVID-19 transmission.²⁷ It remains unknown whether the likelihood of transmission during rebound differs from the likelihood of transmission during the initial infection.²⁷

4C. For immunocompromised patients with rebound COVID-19, is re-treatment or an extended duration of antiviral therapy recommended?

Based on the currently available literature, there is insufficient evidence for the Committee to recommend routine retreatment or an extended duration of antiviral therapy in patients who are immunocompromised.

The optimal management of COVID-19 rebound in patients who are immunocompromised is unclear. Patients with dysregulated immune systems can have different COVID-19 susceptibility and illness courses.^{39,40} Strategies such as extended durations of antiviral therapy, additional courses of antiviral therapy or use of combination therapy have been reported in case reports and case series.^{39–51} However, study design limitations, including differing patient populations across the studies and varying clinical outcomes make it challenging to draw definitive conclusions. Providers should use their clinical judgment to assess a patient’s immunocompromised status, age, comorbidities and vaccination status to manage COVID-19 in people who are immunocompromised. Consultation with an Infectious Disease specialist is recommended for immunocompromised patients with persistent symptoms and viral detection.



5. COVID-19 Reinfection

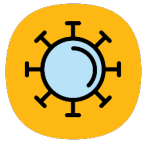
What is the treatment for patients with COVID-19 reinfection?

The Committee recommends that COVID-19 reinfection be assessed and treated as a new infection. The approach to treatment and selection of drug therapy is based on the patient’s presenting signs and symptoms, timing for onset of symptoms, and risk for progression to severe disease.

In Ontario, COVID-19 reinfection is defined in the following ways:

- Laboratory-based reinfection requires evidence such as genome sequencing or variant of concern screening polymerase chain reaction testing that indicates two distinct infections⁵² **OR**
- Time-based reinfection requires the confirmed case of COVID-19 infection occur at least 90 days after the previous infection⁵²

The factors related to COVID-19 reinfection (e.g., prevalence, risk factors, timing, severity) are not fully known and are likely impacted by the circulating variants.¹ For individuals who have had COVID-19, reinfection may occur as the protection from the initial immune response wanes over time.⁵³ Observational data in a highly vaccinated population of patients who had been previously infected with COVID-19 found the reinfection rate to be approximately 10% in the general population during the Omicron era.⁵⁴



6. Post COVID-19 Condition

6A. What is post COVID-19 condition?

Post COVID-19 condition (PCC), also referred to as long COVID, is a heterogeneous syndrome associated with a wide range of symptoms involving multiple organ systems. The World Health Organization defines PCC as the presence of symptoms usually 3 months from the onset of COVID-19 that last for at least 2 months and cannot be explained by an alternative diagnosis.⁵⁵ The literature for risk factors that are associated with PCC development is still evolving.⁵⁶ In Canada, 19% of adults who have been infected with COVID-19 reported experiencing symptoms that are present three or more months after their acute infection.⁵⁷ Over 200 symptoms associated with PCC have been reported⁵⁸. The most common symptoms in adults include fatigue, shortness of breath, trouble sleeping, general pain and discomfort, memory loss, difficulty thinking or concentrating, anxiety and depression.⁵⁶

6B. Does nirmatrelvir/ritonavir or remdesivir treatment of acute infection prevent post COVID-19 condition?

The Committee does not recommend nirmatrelvir/ritonavir or remdesivir to prevent PCC.

Some individuals with COVID-19 experience prolonged symptoms after their acute infection. It is unknown whether nirmatrelvir/ritonavir or remdesivir treatment during the acute phase of COVID-19 infection prevents PCC because observational data for this outcome have been inconsistent.^{58–63} CanTreatCOVID is an open-label, randomized trial currently in progress in Canada to determine whether treatment of acute COVID-19 infection by nirmatrelvir/ritonavir may be effective in preventing PCC.⁶⁴ The Committee will provide additional guidance as more evidence becomes available.

There is still benefit to early antiviral treatment in preventing severe outcomes in high-risk patients with symptomatic mild to moderate COVID-19 during the acute infection to prevent progression to severe outcomes such as emergency department visits, the need for supplemental oxygen, COVID-19-related hospitalization, or death.

6C. Can nirmatrelvir/ritonavir or remdesivir be used to treat people experiencing symptoms of post COVID-19 condition?

The Committee does not recommend nirmatrelvir/ritonavir or remdesivir to treat symptoms of PCC due to the lack of evidence to support their use for this indication.

Nirmatrelvir/ritonavir and remdesivir are antiviral therapies that target actively replicating virus during acute infection. It is unknown whether there is any benefit to offering them weeks or months after acute infection for the purpose of treating PCC symptoms.⁶⁵ There is a paucity of literature to support antiviral treatment for PCC, limited to case reports and case series with varying results that were subject to recall bias.^{66–68} Many of the cases also do not match the current PCC case definition. Clinical studies to treat PCC symptoms are ongoing.⁶⁹ Randomized

controlled trials such as RECOVER-VITAL and STOP-PASC are in progress to determine whether nirmatrelvir/ritonavir may be effective in treating PCC.^{69,70}



7. Proactive Measures

7A. What proactive measures can patients, care partners and health care providers take for the management of COVID-19 therapy before the patient gets sick?

The Committee recommends health care providers identify patients who are at high risk for progression to severe disease, discuss potential treatment options (i.e., nirmatrelvir/ritonavir, remdesivir) with patients and care partners, determine individual eligibility for COVID-19 therapies and develop a treatment plan in advance of potential COVID-19 infection.

The plan should include:

- Patient goals of care
- Where to obtain COVID-19 rapid antigen tests to have on hand at home or where to access COVID-19 testing at a local [COVID-19 testing centre](#)
- Signs and symptoms to prompt COVID-19 testing and when to seek medical attention
- How to contact a health care provider for further evaluation and/or treatment initiation if a COVID-19 test is positive
- Up-to-date renal function tests and other relevant workup as appropriate (e.g., eGFR, ALT)
- A best possible medication history
- Proactive assessment for potential drug-drug interactions to determine whether any contraindications to the COVID-19 drug therapies exist, to develop possible mitigation strategies or to assess for therapeutic alternatives as appropriate
- How to access COVID-19 therapies (i.e., nirmatrelvir/ritonavir, remdesivir) via local pathways so patients can start treatment as quickly as possible

7B. What proactive measures can patients, care partners and health care providers take to prevent COVID-19 infection?

COVID-19 vaccination remains the most effective way to prevent serious outcomes and deaths and should be considered the first line of prevention.¹

The Committee recommends up-to-date COVID-19 vaccination for everyone who is eligible, including those who are moderately or severely immunocompromised.



8. Supplemental Information on Selected Drugs

What is the evidence for the following select drugs to treat acute COVID-19?

The Committee does not recommend the following list of select drugs that have been used for the treatment of COVID-19. Reasons include lack of clinical benefit, loss of benefit due to currently circulating variants or lack of regulatory approval in Canada. Given the dynamic nature of the COVID-19 pandemic, the Committee will provide additional guidance and recommendations as more evidence becomes available.

Table 1: Select Drugs Not Recommended for Treatment of COVID-19

Drug	Clinical Recommendation	Evidence Summary
Casirivimab/imdevimab	Not recommended due to lack of efficacy against circulating variants.	High risk of treatment failure for mild to moderate COVID-19 due to reduced efficacy against the currently circulating Omicron subvariants. ^{1,71}
Colchicine	Not recommended due to lack of benefit and risk of harm.	Randomized controlled trials showed no benefit for reducing hospitalization or mortality, but increased the risk of adverse effects and drug interactions. ^{72,73}
Convalescent plasma	Not recommended due to lack of benefit and risk of harm.	Randomized controlled trials showed no benefit in reducing mortality and inconsistent benefit for reducing hospitalization. ^{74–78}
Corticosteroids (Inhaled)	Not recommended due to lack of benefit.	Randomized controlled trials showed inconsistent benefit in reducing symptom duration, hospitalization or mortality. ^{79–85}
Corticosteroids (Systemic)	Not recommended due to lack of benefit and risk of harm.	Randomized controlled trial showed no benefit in reducing mortality and observational data suggest increased risk of mortality. ^{86,87}
Fluvoxamine	Not recommended due to lack of benefit and risk of harm.	Randomized controlled trials showed no benefit in reducing hospitalization, length of stay or mortality. ^{88,89}

Drug	Clinical Recommendation	Evidence Summary
Hydroxychloroquine	Not recommended due to lack of benefit and risk of harm.	Randomized controlled trials showed no benefit in reducing symptom severity, time to improvement, hospitalization or mortality. ^{90,91}
Ivermectin	Not recommended due to lack of benefit and risk of harm.	Randomized controlled trials showed no benefit in reducing time to recovery, emergency department visits, hospitalization or mortality. ⁹²⁻⁹⁴
Lopinavir/ritonavir	Not recommended due to lack of benefit and risk of harm.	Randomized controlled trial showed no benefit in symptom resolution or hospitalization. ^{95,96}
Metformin	Not recommended due to lack of benefit.	Randomized controlled trials showed no benefit in reducing hospitalization or mortality. ^{94,97}
Molnupiravir	Not recommended because not approved for use in Canada.	Randomized controlled trials showed inconsistent benefit in reducing hospitalization or mortality. ^{98,99} Safety concerns exist in certain populations (e.g., children, pregnant people). ¹ Health Canada has not approved molnupiravir for use in Canada.
Sotrovimab	Not recommended due to lack of efficacy against circulating variants.	Risk of treatment failure for mild to moderate COVID-19 due to reduced efficacy against the currently circulating Omicron subvariants. ^{100,101}
Tixagevimab/cilgavimab	Not recommended due to lack of efficacy against circulating variants.	Risk of failure for pre-exposure prophylaxis and treatment for mild to moderate COVID-19 due to reduced efficacy against the majority of Omicron subvariants. ^{101,102}



Additional Resources

Supplementary Information on Pregnancy and Breastfeeding/Chestfeeding

- [Public Health Agency of Canada: COVID-19 – Pregnancy, Childbirth and Caring for a Newborn](#)
- [The Society of Obstetricians and Gynaecologists of Canada: COVID-19 Resources](#)
- [American College of Obstetricians and Gynecologists: COVID-19 FAQs for Obstetrician-Gynecologists, Obstetrics](#)
- [U.S. National Institutes of Health: COVID-19 Treatment Guidelines on Pregnancy and Lactation](#)
- [U.S. Centers for Disease Control and Prevention: COVID-19 and Breastfeeding](#)

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