



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

Date: September 3, 2024

This document was endorsed 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.

## Table of Contents

- Introduction .....1
- Table of Contents .....1
- 1. Pregnancy .....2
- 2. Breastfeeding or Chestfeeding .....3
- 3. Renal and Hepatic Function Testing .....4
- 4. COVID-19 Post-Exposure Prophylaxis .....5
- 5. COVID-19 Reinfection .....7
- 6. Post COVID-19 Condition .....8
- 7. Proactive Measures .....9
- 8. Supplemental Information on Nirmatrelvir/Ritonavir .....10
- 9. Supplemental Information on Selected Drugs .....11
- Additional Resources .....13
- References .....13



# 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.<sup>1</sup> 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.<sup>2,3</sup>

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.<sup>1,4</sup> 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.<sup>1,4,5</sup> 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.<sup>3</sup>

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.<sup>6-8</sup> 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.<sup>9</sup> 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.<sup>9</sup> 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.<sup>7,9</sup>

## 1B. Can remdesivir be used in pregnant people?

Remdesivir can be used pregnant patients with COVID-19.<sup>1</sup>

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.<sup>1,10</sup> There is a paucity of data for remdesivir use in the first trimester.<sup>10</sup> 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.<sup>1,11</sup> The data from observational studies are mixed on whether remdesivir use is associated with an increase or decrease in preterm delivery or caesarean section.<sup>12,13</sup> Elevated transaminases have been commonly reported in observational studies and post-marketing surveillance databases, but grade 3 (severe or medically significant) abnormalities were uncommon.<sup>1,11,14</sup>



## 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 its nutritional benefits and the protection it may confer to the infant from antibodies and other immunological factors.<sup>15</sup>

Current evidence suggests that breast milk is not a source of COVID-19 infection.<sup>3</sup> 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.<sup>3</sup> 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.<sup>1</sup>

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.<sup>3</sup>

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?

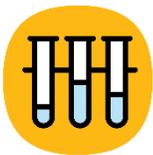
Breastfeeding/chestfeeding can continue while a patient receives nirmatrelvir/ritonavir.<sup>1</sup>

There are extensive data on the safety of ritonavir as part of antiretroviral therapy in pregnant people with HIV.<sup>1</sup> 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.<sup>1,16</sup> There have not been any reports of adverse reactions to ritonavir in breastfed infants.<sup>16</sup> 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.<sup>1,17</sup>

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

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

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.<sup>14,18</sup> One case report estimated the relative infant doses of remdesivir and GS-441524 in breast milk as 0.007% and 1.6%, respectively.<sup>18</sup> No adverse effects have been documented in the small number of infants exposed to remdesivir and its metabolite via breast milk.<sup>14,18</sup>



## 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.<sup>19,20</sup>

### 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.

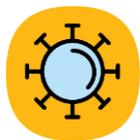
Nirmatrelvir/ritonavir is not recommended for patients with known or suspected severe hepatic impairment (i.e., Child-Pugh Class C) due to a lack of pharmacokinetic and safety data.<sup>21</sup> For patients without recent hepatic function testing results (e.g., bilirubin, INR, serum albumin) where severe 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.<sup>22</sup> 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.<sup>22</sup> 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.<sup>23</sup>

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.<sup>24</sup> 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.<sup>22</sup> 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.<sup>22</sup>



## **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). Nirmatrelvir/ritonavir should be reserved for eligible patients with symptomatic confirmed COVID-19.

To date, the evidence for the use of nirmatrelvir/ritonavir for PEP has been negative. The EPIC-PEP trial evaluated a 5- or 10-day course of nirmatrelvir/ritonavir compared to a 10-day course of placebo in 2,736 adults who had been exposed to a household contact with symptomatic COVID-19.<sup>25</sup> No significant difference was observed between the three treatment groups for the primary efficacy endpoint of symptomatic COVID-19 development through day 14.<sup>25</sup> 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.<sup>25</sup> The primary outcome was consistent among participants who were at high risk for progression to severe COVID-19 and during the periods of delta and omicron predominance.<sup>25</sup>

#### **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.<sup>26</sup> 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.<sup>1,27</sup> The reported rates of rebound COVID-19 range from less than 2% to up to 30% in clinical trials and observational studies.<sup>27–34</sup>

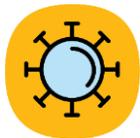
Rebound COVID-19 usually occurs within 2 to 8 days of completing a 5-day course of nirmatrelvir/ritonavir.<sup>1,27</sup> The symptoms associated with rebound COVID-19 are typically mild and self-limiting.<sup>26,28,31</sup> No hospitalizations or deaths have been reported in studies of outpatients who experienced rebound COVID-19.<sup>35</sup> 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.<sup>1,26,29,36</sup> 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.<sup>29,31,37</sup> Rebound COVID-19 has not been found to be associated with reinfection or the development of resistance to nirmatrelvir/ritonavir.<sup>26</sup>

There is currently no evidence for additional treatment with nirmatrelvir/ritonavir or other COVID-19 therapies in cases where COVID-19 rebound is suspected.<sup>1,26</sup> Case reports have reported improvement or resolution of illness and positive COVID-19 test results without additional COVID-19 therapy.<sup>26</sup> 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.<sup>26</sup> It remains unknown whether the likelihood of transmission during rebound differs from the likelihood of transmission during the initial infection.<sup>26</sup>

#### 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.<sup>38,39</sup> 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.<sup>38-50</sup> 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 infections<sup>51</sup> **OR**
- Time-based reinfection requires the confirmed case of COVID-19 infection occur at least 90 days after the previous infection<sup>51</sup>

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.<sup>1</sup> For individuals who have had COVID-19, reinfection may occur as the protection from the initial immune response wanes over time.<sup>52</sup> 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.<sup>53</sup>



## 6. Post COVID-19 Condition

### 6A. What is post COVID-19 condition (PCC)?

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.<sup>54</sup> The literature for risk factors that are associated with PCC development is still evolving.<sup>55</sup> 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.<sup>56</sup> Over 200 symptoms associated with PCC have been reported.<sup>57</sup> 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.<sup>55</sup>

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

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.<sup>57-62</sup> 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.<sup>63</sup> 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 (PCC)?

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 unclear whether there is any benefit to offering them weeks or months after acute infection for the purpose of treating PCC symptoms.<sup>64</sup>

The STOP-PASC randomized controlled trial in adults with moderate to severe PCC symptoms did not demonstrate a significant benefit in the improvement of PCC symptoms for individuals treated with a 15-day course of nirmatrelvir/ritonavir compared to placebo/ritonavir.<sup>65</sup> Another clinical study, RECOVER-VITAL, is in progress to determine whether nirmatrelvir/ritonavir may be effective in treating PCC.<sup>66</sup>

Results from case reports and case series of antiviral treatment for PCC have been inconsistent and were subject to recall bias.<sup>67–69</sup> Many of the cases also do not match the current PCC case definition.



## 7. Proactive Measures

### 7A. What proactive measures can patients, care partners and health care providers take for the management of COVID-19 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 to ensure patients can start the appropriate treatment as quickly as possible.

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, including proactive assessment of drug funding options and applying for drug coverage programs as needed

Consider engaging with high-risk patients:

- During appointments
- Via email or telephone (after identifying patients at high risk for severe disease via electronic medical record search)
- By updating the practice’s website or online booking portal
- By working with community ambassadors and other partners to support outreach to equity-deserving populations

Electronic communications may also be distributed broadly to all patients where feasible.

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

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

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



## **8. Supplemental Information on Nirmatrelvir/Ritonavir**

### **8A. Is there evidence to support the use of nirmatrelvir/ritonavir for COVID-19 symptom alleviation?**

The Committee does not recommend the use of nirmatrelvir/ritonavir to alleviate or shorten symptom of COVID-19 for patients at low risk for severe COVID-19.

The EPIC-SR randomized controlled trial did not find any significant difference between nirmatrelvir/ritonavir and placebo for the primary outcome of self-reported, sustained alleviation of all COVID-19 signs and symptoms in patients who were unvaccinated or who were fully vaccinated with risk factors for progression to severe disease.<sup>70</sup>

### **8B. Would a patient with pre-existing COVID-19 immunity from prior infection and/or vaccination benefit from nirmatrelvir/ritonavir?**

A patient with pre-existing COVID-19 immunity from prior infection and/or vaccination may benefit from nirmatrelvir/ritonavir if they are at high-risk of severe COVID-19 outcomes.

The effectiveness of nirmatrelvir-ritonavir in high-risk populations is likely to vary among the various categories of populations in clinical practice. Not all medical conditions carry the same risk and a greater number of risk factors is associated with a higher risk of severe COVID-19 outcomes.<sup>71–74</sup> Treatment decisions should be individualized based on the prescriber’s assessment of patient risk.

The EPIC-HR trial demonstrated nirmatrelvir/ritonavir treatment was associated with a clinically and statistically significant reduced risk of hospitalization and death compared to placebo in adults at high risk for severe COVID-19 without pre-existing immunity from prior infection or vaccination.<sup>27</sup> With high levels of pre-existing immunity from previous infection and/or vaccination in Ontario, the risk of hospitalization and death due to COVID-19 has decreased.<sup>75,76</sup> Therefore, the expected benefit of nirmatrelvir/ritonavir is likely to be lower compared to the original EPIC-HR trial results. Observational studies in highly vaccinated populations with mild to moderate COVID-19 have found nirmatrelvir/ritonavir use was associated with a decreased risk of COVID-19 related hospitalization or death compared to no nirmatrelvir/ritonavir treatment.<sup>76,77</sup>



## 9. 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
<b>Casirivimab/imdevimab</b>	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. <sup>1,78</sup>
<b>Colchicine</b>	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. <sup>79,80</sup>
<b>Convalescent plasma</b>	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. <sup>81–85</sup>
<b>Corticosteroids (Inhaled)</b>	Not recommended due to lack of benefit.	Randomized controlled trials showed inconsistent benefit in reducing symptom duration, hospitalization or mortality. <sup>86–92</sup>

Drug	Clinical Recommendation	Evidence Summary
<b>Corticosteroids (Systemic)</b>	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. <sup>93,94</sup>
<b>Fluvoxamine</b>	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. <sup>95,96</sup>
<b>Hydroxychloroquine</b>	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. <sup>97,98</sup>
<b>Ivermectin</b>	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. <sup>99-101</sup>
<b>Lopinavir/ritonavir</b>	Not recommended due to lack of benefit and risk of harm.	Randomized controlled trial showed no benefit in symptom resolution or hospitalization. <sup>102,103</sup>
<b>Metformin</b>	Not recommended due to lack of benefit.	Randomized controlled trials showed no benefit in reducing hospitalization or mortality. <sup>101,104</sup>
<b>Molnupiravir</b>	Not recommended because not approved for use in Canada.	Randomized controlled trials showed inconsistent benefit in reducing hospitalization or mortality. <sup>105,106</sup> Safety concerns exist in certain populations (e.g., children, pregnant people). <sup>1</sup> Health Canada has not approved molnupiravir for use in Canada.
<b>Sotrovimab</b>	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. <sup>107,108</sup>
<b>Tixagevimab/cilgavimab</b>	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. <sup>108,109</sup>



## 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](#)
- [U.S. Centers for Disease Control and Prevention: COVID-19 and Breastfeeding](#)

## References

1. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [Internet]. 2023 [cited 2023 Nov 13]. Available from: [files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf](https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf)
2. Centers for Disease Control and Prevention. Pregnant and Recently Pregnant People At Increased Risk for Severe Illness from COVID-19 [Internet]. 2022 [cited 2023 Nov 22]. Available from: [archive.cdc.gov/www\\_cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnant-people.html](https://archive.cdc.gov/www_cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnant-people.html)
3. The American College of Obstetricians and Gynecologists. COVID-19 FAQs for Obstetrician-Gynecologists, Obstetrics [Internet]. 2023 [cited 2023 Nov 22]. Available from: [acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics](https://acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics)
4. Chourasia P, Maringanti BS, Edwards-Fligner M, Gangu K, Bobba A, Sheikh AB, et al. Paxlovid (Nirmatrelvir and Ritonavir) Use in Pregnant and Lactating Woman: Current Evidence and Practice Guidelines—A Scoping Review. *Vaccines*. 2023 Jan 1;11(1):107.
5. Garneau WM, Jones-Beatty K, Ufua MO, Mostafa HH, Klein SL, Burd I, et al. Analysis of Clinical Outcomes of Pregnant Patients Treated With Nirmatrelvir and Ritonavir for Acute SARS-CoV-2 Infection. *JAMA Netw Open*. 2022 Nov 29;5(11):e2244141.
6. Toure BB, Panakam A, Johns SL, Butler SK, Tuomala RE, Diouf K. Oral Nirmatrelvir–Ritonavir Use and Clinical Outcomes in Pregnant Patients With Coronavirus Disease 2019 (COVID-19). *Obstetrics & Gynecology* [Internet]. 2023 Nov 14 [cited 2023 Nov 22]; Available from: [journals.lww.com/10.1097/AOG.0000000000005471](https://journals.lww.com/10.1097/AOG.0000000000005471)
7. Lin CW, Liang YL, Chuang MT, Tseng CH, Tsai PY, Su MT. Clinical outcomes of nirmatrelvir-ritonavir use in pregnant women during the Omicron wave of the coronavirus disease 2019 pandemic. *Journal of Infection and Public Health*. 2023 Dec;16(12):1942–6.
8. Loza A, Farias R, Gavin N, Wagner R, Hammer E, Shields A. Short-term Pregnancy Outcomes After Nirmatrelvir-Ritonavir Treatment for Mild-to-Moderate Coronavirus Disease 2019 (COVID-19). *Obstet Gynecol*. 2022 Sep 1;140(3):447–9.
9. Wong CKH, Lau KTK, Chung MSH, Au ICH, Cheung KW, Lau EHY, et al. Nirmatrelvir/ritonavir use in pregnant women with SARS-CoV-2 Omicron infection: a target trial emulation. *Nat Med* [Internet]. 2023 Nov 1 [cited 2023 Nov 26]; Available from: [nature.com/articles/s41591-023-02674-0](https://nature.com/articles/s41591-023-02674-0)

10. Budi DS, Pratama NR, Wafa IA, Putra M, Wardhana MP, Wungu CDK. Remdesivir for pregnancy: A systematic review of antiviral therapy for COVID-19. *Heliyon*. 2022 Jan;8(1):e08835.
11. Gutierrez R, Mendez-Figueroa H, Biebighauser JG, Bhalwal A, Pineles BL, Chauhan SP. Remdesivir use in pregnancy during the SARS-CoV-2 pandemic. *J Matern Fetal Neonatal Med*. 2022 Dec;35(25):9445–51.
12. Remdesivir (Veklury®). In: *Mother To Baby | Fact Sheets* [Internet]. Brentwood (TN): Organization of Teratology Information Specialists (OTIS); 1994 [cited 2023 Nov 27]. Available from: [ncbi.nlm.nih.gov/books/NBK582932/](https://ncbi.nlm.nih.gov/books/NBK582932/)
13. Di Gennaro F, Guido G, Frallonardo L, Segala FV, De Nola R, Damiani GR, et al. Efficacy and safety of therapies for COVID-19 in pregnancy: a systematic review and meta-analysis. *BMC Infect Dis*. 2023 Nov 9;23(1):776.
14. Jorgensen SC, Tabbara N, Burry L. A review of COVID-19 therapeutics in pregnancy and lactation. *Obstet Med*. 2022 Dec;15(4):225–32.
15. Centers of Disease Control and Prevention. COVID-19 and Breastfeeding [Internet]. 2021 [cited 2024 Feb 2]. Available from: [cdc.gov/breastfeeding/breastfeeding-special-circumstances/maternal-or-infant-illnesses/covid-19-and-breastfeeding.html](https://cdc.gov/breastfeeding/breastfeeding-special-circumstances/maternal-or-infant-illnesses/covid-19-and-breastfeeding.html)
16. Drugs and Lactation Database (LactMed®). Ritonavir [Internet]. National Institute of Child Health and Human Development; 2023 [cited 2023 Nov 23]. Available from: [ncbi.nlm.nih.gov/books/NBK501541/](https://ncbi.nlm.nih.gov/books/NBK501541/)
17. Drugs and Lactation Database (LactMed®). Nirmatrelvir [Internet]. National Institute of Child Health and Human Development; 2023 [cited 2023 Nov 23]. Available from: [ncbi.nlm.nih.gov/books/NBK576869/](https://ncbi.nlm.nih.gov/books/NBK576869/)
18. Remdesivir. In: *Drugs and Lactation Database (LactMed®)* [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006 [cited 2023 Dec 10]. Available from: [ncbi.nlm.nih.gov/books/NBK556881/](https://ncbi.nlm.nih.gov/books/NBK556881/)
19. Health Quality Ontario. Aspartate Aminotransferase Testing [Internet]. 2013 [cited 2023 Nov 30]. Available from: [hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment/Reviews-And-Recommendations/Aspartate-Aminotransferase-Testing](https://hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment/Reviews-And-Recommendations/Aspartate-Aminotransferase-Testing)
20. Island Health. Using Labs Wisely at Island Health [Internet]. [cited 2023 Dec 12]. Available from: [medicalstaff.islandhealth.ca/sites/default/files/working-for-change/choosing-wisely/using-labs-wisely- unbundling.pdf](https://medicalstaff.islandhealth.ca/sites/default/files/working-for-change/choosing-wisely/using-labs-wisely- unbundling.pdf)
21. Pfizer Canada ULC. Paxlovid Product Monograph [Internet]. 2023 [cited 2023 Nov 20]. Available from: [pdf.hres.ca/dpd\\_pm/00072671.PDF](https://pdf.hres.ca/dpd_pm/00072671.PDF)
22. Gilead Sciences Canada. Veklury Product Monograph [Internet]. 2023 [cited 2023 Nov 20]. Available from: [pdf.hres.ca/dpd\\_pm/00073413.PDF](https://pdf.hres.ca/dpd_pm/00073413.PDF)
23. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med*. 2022 Jan 27;386(4):305–15.
24. Remdesivir. In: *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012 [cited 2023 Dec 12]. Available from: [ncbi.nlm.nih.gov/books/NBK564049/](https://ncbi.nlm.nih.gov/books/NBK564049/)
25. Hammond J, Yunis C, Fountaine RJ, Luscan G, Burr AM, Zhang W, et al. Oral Nirmatrelvir–Ritonavir as Postexposure Prophylaxis for Covid-19. *N Engl J Med*. 2024 Jul 18;391(3):224–34.

26. Centers for Disease Control and Prevention. COVID-19 Rebound After Paxlovid Treatment [Internet]. 2022 [cited 2023 Nov 23]. Available from: [emergency.cdc.gov/han/2022/pdf/cdc\\_han\\_467.Pdf](https://emergency.cdc.gov/han/2022/pdf/cdc_han_467.Pdf)
27. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. *N Engl J Med*. 2022 Apr 14;386(15):1397–408.
28. Sebők S, Gyires K. Long COVID and possible preventive options. *Inflammopharmacology*. 2023 Dec;31(6):2807–17.
29. Meyerowitz EA, Li Y. Review: The Landscape of Antiviral Therapy for COVID-19 in the Era of Widespread Population Immunity and Omicron-Lineage Viruses. *Clin Infect Dis*. 2023 Nov 9;ciad685.
30. Pandit JA, Radin JM, Chiang DC, Spencer EG, Pawelek JB, Diwan M, et al. The Coronavirus Disease 2019 Rebound Study: A Prospective Cohort Study to Evaluate Viral and Symptom Rebound Differences in Participants Treated With Nirmatrelvir Plus Ritonavir Versus Untreated Controls. *Clin Infect Dis*. 2023 Jul 5;77(1):25–31.
31. Petrakis V, Rafailidis P, Trypsianis G, Papazoglou D, Panagopoulos P. The Antiviral Effect of Nirmatrelvir/Ritonavir during COVID-19 Pandemic Real-World Data. *Viruses*. 2023 Apr 16;15(4):976.
32. Lai CC, Hsueh PR. Coronavirus disease 2019 rebounds following nirmatrelvir/ritonavir treatment. *J Med Virol*. 2023 Feb;95(2):e28430.
33. Ranganath N, O’Horo JC, Challener DW, Tullledge-Scheitel SM, Pike ML, O’Brien M, et al. Rebound Phenomenon After Nirmatrelvir/Ritonavir Treatment of Coronavirus Disease 2019 (COVID-19) in High-Risk Persons. *Clin Infect Dis*. 2023 Feb 8;76(3):e537–9.
34. Wong GLH, Yip TCF, Lai MSM, Wong VWS, Hui DSC, Lui GCY. Incidence of Viral Rebound After Treatment With Nirmatrelvir-Ritonavir and Molnupiravir. *JAMA Netw Open*. 2022 Dec 1;5(12):e2245086.
35. Smith DJ, Lambrou A, Patel P. SARS-CoV-2 Rebound With and Without Use of COVID-19 Oral Antivirals. *MMWR Morb Mortal Wkly Rep*. 2023 Dec 22;72(51):1357–64.
36. British Columbia COVID-19 Therapeutics Committee, COVID-19 Therapeutics Review and Advisory Working Group. Antimicrobial and Immunomodulatory Therapy in Adult Patients with COVID-19 [Internet]. 2023 [cited 2023 Nov 14]. Available from: [bccdc.ca/Health-Professionals-Site/Documents/Antimicrobial-Immunomodulatory-Therapy-adults.pdf](https://bccdc.ca/Health-Professionals-Site/Documents/Antimicrobial-Immunomodulatory-Therapy-adults.pdf)
37. Wong CKH, Lau KTK, Au ICH, Lau EHY, Poon LLM, Hung IFN, et al. Viral burden rebound in hospitalised patients with COVID-19 receiving oral antivirals in Hong Kong: a population-wide retrospective cohort study. *Lancet Infect Dis*. 2023 Jun;23(6):683–95.
38. Guo W, Zheng Y, Feng S. Omicron related COVID-19 prevention and treatment measures for patients with hematological malignancy and strategies for modifying hematologic treatment regimes. *Front Cell Infect Microbiol*. 2023;13:1207225.
39. DeWolf S, Laracy JC, Perales MA, Kamboj M, van den Brink MRM, Vardhana S. SARS-CoV-2 in immunocompromised individuals. *Immunity*. 2022 Oct 11;55(10):1779–98.
40. Graziani L, Gori L, Manciuilli T, Basile G, Campolmi I, Borchi B, et al. Successful use of nirmatrelvir/ritonavir in immunocompromised patients with persistent and/or relapsing COVID-19. *J Antimicrob Chemother*. 2023 Feb 1;78(2):555–8.
41. Trottier CA, Wong B, Kohli R, Boomsma C, Magro F, Kher S, et al. Dual Antiviral Therapy for Persistent Coronavirus Disease 2019 and Associated Organizing Pneumonia in an Immunocompromised Host. *Clin Infect Dis*. 2023 Mar 4;76(5):923–5.

42. Mikulska M, Sepulcri C, Dentone C, Magne F, Balletto E, Baldi F, et al. Triple Combination Therapy With 2 Antivirals and Monoclonal Antibodies for Persistent or Relapsed Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Immunocompromised Patients. *Clin Infect Dis*. 2023 Jul 26;77(2):280–6.
43. Caso JM, Fernández-Ruiz M, López-Medrano F, Caro-Teller JM, Lizasoain M, San-Juan R, et al. Nirmatrelvir/ritonavir for the treatment of immunocompromised adult patients with early-stage symptomatic COVID-19: A real-life experience. *J Med Virol*. 2023 Sep;95(9):e29082.
44. Basoulis D, Tsakanikas A, Gkoufa A, Bitsani A, Karamanakos G, Mastrogianni E, et al. Effectiveness of Oral Nirmatrelvir/Ritonavir vs. Intravenous Three-Day Remdesivir in Preventing Progression to Severe COVID-19: A Single-Center, Prospective, Comparative, Real-Life Study. *Viruses*. 2023 Jul 7;15(7):1515.
45. Chan M, Linn MMN, O’Hagan T, Guerra-Assunção JA, Lackenby A, Workman S, et al. Persistent SARS-CoV-2 PCR Positivity Despite Anti-viral Treatment in Immunodeficient Patients. *J Clin Immunol*. 2023 Aug;43(6):1083–92.
46. Moso MA, Sasadeusz J, Morrissey CO, Bond K, Guy S, Slavin MA, et al. Survey of treatment practices for immunocompromised patients with COVID-19 in Australasia. *Intern Med J*. 2023 Apr;53(4):619–24.
47. Ambati S, Ali B, Seddon O, Godkin A, Scurr M, Moore C, et al. Resolution of persistent SARS-CoV-2 infection with prolonged intravenous remdesivir and vaccination in a patient post CAR-T. *Int J Hematol*. 2023 May;117(5):765–8.
48. Marangoni D, Antonello RM, Coppi M, Palazzo M, Nassi L, Strega N, et al. Combination regimen of nirmatrelvir/ritonavir and molnupiravir for the treatment of persistent SARS-CoV-2 infection: A case report and a scoping review of the literature. *Int J Infect Dis*. 2023 Aug;133:53–6.
49. Tadmor T, Melamed G, Patalon T, Alapi H, Rokach L. Rebound of COVID-19 infection in patients with chronic lymphocytic leukemia treated for SARS-CoV-2 with Nirmatrelvir/Ritonavir or Molnupiravir. *Leuk Lymphoma*. 2023 May;64(5):1054–6.
50. Schminke L, Fleck M. Delayed COVID-19 rebound following nirmatrelvir/ritonavir treatment in B-cell-depleted patients. *Int J Rheum Dis*. 2023 Feb;26(2):396–7.
51. Ontario Ministry of Health. Case Definitions and Disease Specific Information [Internet]. 2023 [cited 2023 Nov 28]. Available from: [health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/2019\\_case\\_definition.pdf](https://health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/2019_case_definition.pdf)
52. Centers for Disease Control and Prevention. What is COVID-19 Reinfection? [Internet]. 2023 [cited 2023 Dec 12]. Available from: [cdc.gov/coronavirus/2019-ncov/your-health/reinfection.html](https://cdc.gov/coronavirus/2019-ncov/your-health/reinfection.html)
53. Eythorsson E, Runolfssdottir HL, Ingvarsson RF, Sigurdsson MI, Palsson R. Rate of SARS-CoV-2 Reinfection During an Omicron Wave in Iceland. *JAMA Netw Open*. 2022 Aug 3;5(8):e2225320.
54. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus [Internet]. 2021 [cited 2023 Nov 29]. Available from: [iris.who.int/bitstream/handle/10665/345824/WHO-2019-nCoV-Post-COVID-19-condition-Clinical-case-definition-2021.1-eng.pdf?sequence=1](https://iris.who.int/bitstream/handle/10665/345824/WHO-2019-nCoV-Post-COVID-19-condition-Clinical-case-definition-2021.1-eng.pdf?sequence=1)
55. World Health Organization. Post COVID-19 condition (Long COVID) [Internet]. World Health Organization; 2023 [cited 2023 Dec 12]. Available from: [who.int/europe/news-room/fact-sheets/item/post-covid-19-condition](https://who.int/europe/news-room/fact-sheets/item/post-covid-19-condition)

56. Kuang S, Earl S, Clarke J, Zakaria D, Demers A, Aziz S. Experiences of Canadians with long-term symptoms following COVID-19 [Internet]. 2023. Available from: [www150.statcan.gc.ca/n1/pub/75-006-x/2023001/article/00015-eng.pdf](http://www150.statcan.gc.ca/n1/pub/75-006-x/2023001/article/00015-eng.pdf)
57. Chuang M, Wu J, Liu T, Hsu W, Tsai Y, Huang P, et al. Efficacy of nirmatrelvir and ritonavir for post-acute COVID-19 sequelae beyond 3 months of SARS-CoV-2 infection. *Journal of Medical Virology*. 2023 Apr;95(4):e28750.
58. Congdon S, Narrowe Z, Yone N, Gunn J, Deng Y, Nori P, et al. Nirmatrelvir/ritonavir and risk of long COVID symptoms: a retrospective cohort study. *Sci Rep*. 2023 Nov 11;13(1):19688.
59. Xie Y, Choi T, Al-Aly Z. Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition. *JAMA Intern Med*. 2023 Jun 1;183(6):554.
60. Bertuccio P, Degli Antoni M, Minisci D, Amadasi S, Castelli F, Odone A, et al. The impact of early therapies for COVID-19 on death, hospitalization and persisting symptoms: a retrospective study. *Infection* [Internet]. 2023 Apr 6 [cited 2023 Nov 17]; Available from: [link.springer.com/10.1007/s15010-023-02028-5](https://link.springer.com/10.1007/s15010-023-02028-5)
61. Boglione L, Meli G, Poletti F, Rostagno R, Moglia R, Cantone M, et al. Risk factors and incidence of long-COVID syndrome in hospitalized patients: does remdesivir have a protective effect? *QJM: An International Journal of Medicine*. 2022 Jan 9;114(12):865–71.
62. Nevalainen OPO, Horstia S, Laakkonen S, Rutanen J, Mustonen JMJ, Kalliala IEJ, et al. Effect of remdesivir post hospitalization for COVID-19 infection from the randomized SOLIDARITY Finland trial. *Nat Commun*. 2022 Oct 18;13(1):6152.
63. MAP Centre for Urban Health Solutions. Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings (CanTreatCOVID) [Internet]. 2023 [cited 2024 Feb 2]. Available from: [cantreatcovid.org/about/](http://cantreatcovid.org/about/)
64. Alberta Health Services. Nirmatrelvir/ritonavir (Paxlovid™) Outpatient Treatment [Internet]. 2023 [cited 2023 Dec 12]. Available from: [albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-paxlovid-faq-hcw.pdf](http://albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-paxlovid-faq-hcw.pdf)
65. Geng LN, Bonilla H, Hedlin H, Jacobson KB, Tian L, Jagannathan P, et al. Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection: The STOP-PASC Randomized Clinical Trial. *JAMA Intern Med*. 2024 Jun 7:e242007.
66. National Institutes of Health. NIH launches long COVID clinical trials through RECOVER Initiative, opening enrollment [Internet]. 2023 [cited 2023 Nov 28]. Available from: [nih.gov/news-events/news-releases/nih-launches-long-covid-clinical-trials-through-recover-initiative-opening-enrollment](https://nih.gov/news-events/news-releases/nih-launches-long-covid-clinical-trials-through-recover-initiative-opening-enrollment)
67. Cohen AK, Jaudon TW, Schurman EM, Kava L, Vogel JM, Haas-Godsil J, et al. Impact of extended-course oral nirmatrelvir/ritonavir (Paxlovid) in established Long COVID: Case series and research considerations. *Res Sq*. 2023 Sep 20;rs.3.rs-3359429.
68. Peluso MJ, Anglin K, Durstenfeld MS, Martin JN, Kelly JD, Hsue PY, et al. Effect of Oral Nirmatrelvir on Long COVID Symptoms: 4 Cases and Rationale for Systematic Studies. *Pathog Immun*. 2022;7(1):95–103.
69. Geng LN, Bonilla HF, Shafer RW, Miglis MG, Yang PC. The Use of Nirmatrelvir-ritonavir in a Case of Breakthrough Long COVID. *Explor Res Hypothesis Med*. 2023 Jan 13;8(4):394–6.
70. Hammond J, Fountaine RJ, Yunis C, Fleishaker D, Almas M, Bao W, et al. Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with Covid-19. *N Engl J Med*. 2024 Apr 4;390(13):1186–95.

71. Canadian Agency for Drugs and Technologies in Health. Nirmatrelvir-Ritonavir (Paxlovid) [Internet]. 2024 Apr 30 [cited 2024 Jul 2];4(4). Available from: [canjhealthtechnol.ca/index.php/cjht/article/view/SR0808](https://canjhealthtechnol.ca/index.php/cjht/article/view/SR0808)
72. Center for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals [Internet]. 2024 [cited 2024 May 16]. Available from: [cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html](https://cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html)
73. U.S. Department of Health and Human Services. Federal Response to COVID-19: Therapeutics Clinical Implementation Guide [Internet]. 2023 [cited 2024 Jan 30]. Available from: [aspr.hhs.gov/COVID-19/Therapeutics/Documents/USG-COVID19-Tx-Playbook.pdf](https://aspr.hhs.gov/COVID-19/Therapeutics/Documents/USG-COVID19-Tx-Playbook.pdf)
74. Agrawal U, Bedston S, McCowan C, Oke J, Patterson L, Robertson C, et al. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. *Lancet*. 2022 Oct 15;400(10360):1305–20.
75. COVID-19 Immunity Task Force. Seroprevalence in Canada [Internet]. 2024 [cited 2024 May 16]. Available from: [covid19immunitytaskforce.ca/seroprevalence-in-canada/](https://covid19immunitytaskforce.ca/seroprevalence-in-canada/)
76. Ombelet S, Castanares-Zapatero D, Desimpel F, Hulstaert F, Stordeur S, Roberfroid D. Effectiveness of nirmatrelvir-ritonavir on severe outcomes of COVID-19 in the era of vaccination and Omicron: An updated meta-analysis. *Journal of Medical Virology*. 2024 Feb;96(2):e29434.
77. Schwartz KL, Wang J, Tadrous M, Langford BJ, Daneman N, Leung V, et al. Population-based evaluation of the effectiveness of nirmatrelvir-ritonavir for reducing hospital admissions and mortality from COVID-19. *CMAJ*. 2023 Feb 13;195(6):E220–6.
78. Health Canada. Casirivimab and Imdevimab – High Risk of Treatment Failure Due to Circulation of SARS-CoV-2 Omicron Variant [Internet]. 2022 [cited 2023 Dec 18]. Available from: [recalls-rappels.canada.ca/en/alert-recall/casirivimab-and-imdevimab-high-risk-treatment-failure-due-circulation-sars-cov-2](https://recalls-rappels.canada.ca/en/alert-recall/casirivimab-and-imdevimab-high-risk-treatment-failure-due-circulation-sars-cov-2)
79. Tardif JC, Bouabdallaoui N, L’Allier PL, Gaudet D, Shah B, Pillinger MH, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med*. 2021 Aug;9(8):924–32.
80. Dorward J, Yu LM, Hayward G, Saville BR, Gbinigie O, Van Hecke O, et al. Colchicine for COVID-19 in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial. *Br J Gen Pract*. 2022 Jul;72(720):e446–55.
81. Korley FK, Durkalski-Mauldin V, Yeatts SD, Schulman K, Davenport RD, Dumont LJ, et al. Early Convalescent Plasma for High-Risk Outpatients with Covid-19. *N Engl J Med*. 2021 Nov 18;385(21):1951–60.
82. Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. *N Engl J Med*. 2021 Feb 18;384(7):610–8.
83. Sullivan DJ, Gebo KA, Shoham S, Bloch EM, Lau B, Shenoy AG, et al. Early Outpatient Treatment for Covid-19 with Convalescent Plasma. *N Engl J Med*. 2022 May 5;386(18):1700–11.
84. Alemany A, Millat-Martinez P, Corbacho-Monné M, Malchair P, Ouchi D, Ruiz-Comellas A, et al. High-titre methylene blue-treated convalescent plasma as an early treatment for outpatients with COVID-19: a randomised, placebo-controlled trial. *Lancet Respir Med*. 2022 Mar;10(3):278–88.
85. Gharbharan A, Jordans C, Zwaginga L, Papageorgiou G, van Geloven N, van Wijngaarden P, et al. Outpatient convalescent plasma therapy for high-risk patients with early COVID-19: a randomized placebo-controlled trial. *Clin Microbiol Infect*. 2023 Feb;29(2):208–14.

86. Ramakrishnan S, Nicolau DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *Lancet Respir Med*. 2021 Jul;9(7):763–72.
87. Clemency BM, Varughese R, Gonzalez-Rojas Y, Morse CG, Phipatanakul W, Koster DJ, et al. Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA Intern Med*. 2022 Jan 1;182(1):42–9.
88. Ezer N, Belga S, Daneman N, Chan A, Smith BM, Daniels SA, et al. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: CONTAIN phase II randomised controlled trial. *BMJ*. 2021 Nov 2;375:e068060.
89. Duvignaud A, Lhomme E, Onaisi R, Sitta R, Gelley A, Chastang J, et al. Inhaled ciclesonide for outpatient treatment of COVID-19 in adults at risk of adverse outcomes: a randomised controlled trial (COVERAGE). *Clin Microbiol Infect*. 2022 Jul;28(7):1010–6.
90. Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group, Naggie S. Inhaled Fluticasone for Outpatient Treatment of Covid-19: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial. *medRxiv*. 2022 Aug 11;2022.07.12.22277548.
91. Reis G, Dos Santos Moreira Silva EA, Medeiros Silva DC, Thabane L, de Souza Campos VH, Ferreira TS, et al. Oral Fluvoxamine With Inhaled Budesonide for Treatment of Early-Onset COVID-19 : A Randomized Platform Trial. *Ann Intern Med*. 2023 May;176(5):667–75.
92. Yu LM, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021 Sep 4;398(10303):843–55.
93. Crothers K, DeFaccio R, Tate J, Alba PR, Goetz MB, Jones B, et al. Dexamethasone in hospitalised COVID-19 patients not on intensive respiratory support. *Eur Respir J*. 2022 Jul;60(1):2102532.
94. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021 Feb 25;384(8):693–704.
95. Stewart TG, Rebolledo PA, Mourad A, Lindsell CJ, Boulware DR, McCarthy MW, et al. Higher-Dose Fluvoxamine and Time to Sustained Recovery in Outpatients With COVID-19: The ACTIV-6 Randomized Clinical Trial. *JAMA*. 2023 Nov 17;e2323363.
96. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health*. 2022 Jan;10(1):e42–51.
97. Mitjà O, Corbacho-Monné M, Ubals M, Tebé C, Peñafiel J, Tobias A, et al. Hydroxychloroquine for Early Treatment of Adults With Mild Coronavirus Disease 2019: A Randomized, Controlled Trial. *Clin Infect Dis*. 2021 Dec 6;73(11):e4073–81.
98. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial. *Ann Intern Med*. 2020 Oct 20;173(8):623–31.
99. Reis G, Silva EASM, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of Early Treatment with Ivermectin among Patients with Covid-19. *N Engl J Med*. 2022 May 5;386(18):1721–31.
100. Naggie S, Boulware DR, Lindsell CJ, Stewart TG, Gentile N, Collins S, et al. Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19: A Randomized Clinical Trial. *JAMA*. 2022 Oct 25;328(16):1595–603.

101. Bramante CT, Huling JD, Tignanelli CJ, Buse JB, Liebovitz DM, Nicklas JM, et al. Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19. *N Engl J Med*. 2022 Aug 18;387(7):599–610.
102. Kaizer AM, Shapiro NI, Wild J, Brown SM, Cwik BJ, Hart KW, et al. Lopinavir/ritonavir for treatment of non-hospitalized patients with COVID-19: a randomized clinical trial. *Int J Infect Dis*. 2023 Mar;128:223–9.
103. Reis G, Moreira Silva EADS, Medeiros Silva DC, Thabane L, Singh G, Park JJH, et al. Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19: The TOGETHER Randomized Clinical Trial. *JAMA Netw Open*. 2021 Apr 1;4(4):e216468.
104. Reis G, Dos Santos Moreira Silva EA, Medeiros Silva DC, Thabane L, Cruz Milagres A, Ferreira TS, et al. Effect of early treatment with metformin on risk of emergency care and hospitalization among patients with COVID-19: The TOGETHER randomized platform clinical trial. *Lancet Reg Health Am*. 2022 Feb;6:100142.
105. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N Engl J Med*. 2022 Feb 10;386(6):509–20.
106. Butler CC, Hobbs FDR, Gbinigie OA, Rahman NM, Hayward G, Richards DB, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet*. 2023 Jan 28;401(10373):281–93.
107. Health Canada. Sotrovimab for Injection - Risk of Treatment Failure due to Circulation of SARS-CoV-2 Omicron BA.2 Subvariant [Internet]. 2022 [cited 2023 Nov 27]. Available from: [recalls-rappels.canada.ca/en/alert-recall/sotrovimab-injection-risk-treatment-failure-due-circulation-sars-cov-2-omicron-ba2](https://recalls-rappels.canada.ca/en/alert-recall/sotrovimab-injection-risk-treatment-failure-due-circulation-sars-cov-2-omicron-ba2)
108. BC Centre for Disease Control. Clinical Practice Guide for the Use of Therapeutics in Mild-Moderate COVID-19 [Internet]. 2023 [cited 2023 Nov 20]. Available from: [bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/ClinicalPracticeGuide\\_Therapeutics\\_MildModerateCOVID.pdf](https://bccdc.ca/Health-Professionals-Site/Documents/COVID-treatment/ClinicalPracticeGuide_Therapeutics_MildModerateCOVID.pdf)
109. Health Canada. EVUSHELD (tixagevimab and cilgavimab for injection) - Risk of Prophylaxis or Treatment Failure due to Antiviral Resistance to specific SARS-CoV-2 Subvariants [Internet]. 2022 [cited 2023 Dec 15]. Available from: [recalls-rappels.canada.ca/en/alert-recall/evusheld-tixagevimab-and-cilgavimab-injection-risk-prophylaxis-or-treatment-failure-0](https://recalls-rappels.canada.ca/en/alert-recall/evusheld-tixagevimab-and-cilgavimab-injection-risk-prophylaxis-or-treatment-failure-0)

Need this information in an accessible format? 1-877-280-8538, TTY 1-800-855-0511, [info@ontariohealth.ca](mailto:info@ontariohealth.ca).

This document is technical in nature and is available in English only due to its limited targeted audience. This publication has been exempted from translation under the French Language Services Act. For questions or support regarding this document, please contact [info@ontariohealth.ca](mailto:info@ontariohealth.ca).

Ce document est de nature technique et est disponible en anglais seulement en raison de son public cible limité. Ce document a été exempté de la traduction en vertu de la Loi sur les services en français. Pour toute question ou de l'aide concernant ce document, veuillez contacter [info@ontariohealth.ca](mailto:info@ontariohealth.ca).