INFORMATION FOR HEALTHCARE PROVIDERS: Safety considerations for nirmatrelvir/ritonavir (Paxlovid®) use in persons living with HIV whether or not on antiretroviral treatment, or persons at risk of HIV while on PrEP who are diagnosed with COVID-19 infection

BRITISH COLUMBIA CENTRE *for* EXCELLENCE *in* HIV/AIDS

The COVID-19 therapy Paxlovid® consists of the antiviral medication nirmatrelvir co-packaged with the pharmacokinetic enhancer ("booster") ritonavir, taken as a twice daily, oral, five-day treatment course, with dosage adjustment required for renal impairment (see prescribing information).[1,2]

Nirmatrelvir/ritonavir treatment is initiated as soon as possible following a positive SARS-CoV-2 test result. Eligibility criteria for nirmatrelvir/ritonavir vary between Canadian provinces and will likely evolve over time. Also, eligibility in British Columbia may be expanded as drug supply increases. Therefore, prescribers are strongly encouraged to refer to current nirmatrelvir/ritonavir prescribing information and local guidelines for treatment eligibility and general contraindications/precautions. In British Columbia, see the BC Centre for Disease Control website:
http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/clinical-care/treatments

Theoretical risk of HIV-1 drug resistance mutations in persons with undiagnosed or untreated HIV [1]

- Nirmatrelvir/ritonavir prescribing information cautions that, because ritonavir has antiretroviral activity, persons with undiagnosed or uncontrolled HIV-1 infection might be at risk for developing drug resistance mutations to HIV protease inhibitors.

- Given the low dose of ritonavir and the short-duration treatment course of nirmatrelvir/ritonavir for COVID-19, the risk of emergent HIV drug resistance mutations in the presence of uncontrolled HIV infection is low. If nirmatrelvir/ritonavir is clinically indicated for COVID-19, do not delay treatment initiation while awaiting HIV-related test results. If there is a suspicion of undiagnosed/ untreated HIV infection, follow up with diagnostic screening and/or (re-)engagement with HIV care as soon as possible.

- HIV infected individuals who are diagnosed with COVID-19, and who meet current COVID-19 Therapeutics Committee (CTC) eligibility criteria for nirmatrelvir/ritonavir should be considered eligible to receive nirmatrelvir/ritonavir therapy, regardless of ARV treatment status, viral load level, or CD4 cell count. (http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/clinical-care/treatments)

General drug interaction considerations: [1-4]

Nirmatrelvir/ritonavir has the potential to have numerous clinically important drug interactions, largely related to the ritonavir component (strong CYP3A inhibitor). Healthcare providers are advised to conduct a detailed medication review (PharmaNet review and medication history including prescription and non-prescription medication use – of note, PharmaNet captures most but not all the antiretroviral prescriptions in British Columbia) and check for drug interactions using a current drug interaction resource, such as University of Liverpool COVID-19 Drug Interactions https://www.covid19-druginteractions.org/, which is current and considers drug interactions in the context of the short treatment duration of nirmatrelvir/ritonavir.

Co-administration with Antiretroviral therapy (ART) or Pre-exposure prophylaxis (PrEP) medications
The combination of nirmatrelvir/ritonavir with antiretroviral HIV medications has not been evaluated in clinical studies, and there is limited clinical experience. Prescribers are encouraged to individualize risk-benefit assessment, considering potential drug interactions, comorbidities (including kidney disease), and risk factors for severe COVID-19 disease.

In general, ART or PrEP may be continued without interruption during nirmatrelvir/ritonavir therapy. Specific clinical scenarios include:

1. **ART regimen includes the "booster" ritonavir or cobicistat:** [1,3,4] Paxlovid® prescribing information recommends taking nirmatrelvir/ritonavir in addition to the usual ART regimen, without dose adjustment (i.e. short-term additive doses of "booster" components).

    - The additive ritonavir and/or cobicistat doses from combined ART and COVID-19 treatments may be associated with short-term increased side effects such as gastrointestinal upset.

2. **ART regimen or PrEP medication includes tenofovir alafenamide:** [3,4] No dose adjustment of tenofovir alafenamide (TAF) is required. Continue the usual ART or PrEP medication schedule.

    - Ritonavir inhibits the transporter P-gp and may increase the absorption of tenofovir from the gut, increasing tenofovir levels. Although TAF prescribing information recommends a 10 mg daily dose when co-administered with ritonavir, persons whose ART or PrEP regimen includes TAF 25 mg daily do NOT require TAF dose adjustment during short-term nirmatrelvir/ritonavir therapy.[4]

3. **ART regimen includes hepatic (CYP3A) enzyme-inducing antiretrovirals:** [3,4] Nirmatrelvir/ritonavir may be given together with efavirenz or nevirapine without dose adjustment.

    - The antiretrovirals nevirapine and efavirenz are moderate inducers of CYP3A4 and could potentially decrease levels of nirmatrelvir/ritonavir. Although co-administration has not been studied, drug interaction resources[3,4] suggest the Paxlovid® 100 mg twice daily ritonavir dose likely offsets a potential decrease in ritonavir levels secondary to efavirenz or nevirapine CYP3A induction.[3]

4. **ART regimen includes maraviroc:** [3-5] For ART regimens including ritonavir or cobicistat, the usual maraviroc dose is 150 mg twice daily. Persons whose current maraviroc dose is a total of 300 mg daily should continue their usual dose during nirmatrelvir/ritonavir therapy.

    - Persons taking an unboosted ART regimen with a total maraviroc dose >300 mg daily should continue their usual dose. If significant maraviroc side effects develop (diarrhea, nausea, headache, hypotension), a temporary maraviroc dose reduction may be considered.[4] Consult the HIV care provider/ HIV pharmacist (and continue the usual maraviroc dose while awaiting guidance).

Resources:
REACH line (Rapid Expert Advice and Consultation for HIV) for healthcare providers **1-800-665-7677**
Upon dialing this number, healthcare providers may speak to:

- An HIV Infectious Disease Specialist
- A Family Physician who is experienced in HIV management
- An HIV-experienced Pharmacist*

*For consultation regarding antiretroviral drug interactions with nirmatrelvir/ritonavir in persons receiving HIV treatment or prevention therapies a pharmacist at **St. Paul's Hospital Ambulatory Pharmacy** may also be reached at: **1-888-511-6222** (Monday to Friday daytime and urgent issues after hours)

The current version of this document is available for download at:
http://www.bccfe.ca/publications/centre-documents/bc-cfe-guidelines-use-paxlovid-and-arvs

References:

1. Paxlovid Product Monograph. Pfizer Canada ULC. Kirkland, Quebec. Last updated 17-Jan-2022. Available at: https://pdf.hres.ca/dpd_pm/00064313.PDF

2. Health Product Risk Communication: PAXLOVID (nirmatrelvir and ritonavir) - Dosing and Dispensing in Renal Impairment, Risk of Serious Adverse Reactions Due to Drug Interactions, and English-Only Labels. Government of Canada. Last updated 17-Jan-2022. Accessed 17-Jan-2022. Available at https://recalls-rappels.canada.ca/en/alert-recall/paxlovid-nirmatrelvir-and-ritonavir-dosing-and-dispensing-renal-impairment-risk

3. Liverpool drug interactions group. COVID-19 Drug Interactions. University of Liverpool. Accessed 17-Jan-2022. Available at: https://www.covid19-druginteractions.org/

4. HIV/HCV Drug Therapy Guide. Immunodeficiency Clinic at UHN Toronto General Hospital. Accessed 17-Jan-2022. Available at: https://hivclinic.ca/wp-content/plugins/php/app1.php

5. Celsentri Product Monograph. ViiV Healthcare ULC. Laval Quebec. Last updated 5-Jul-2019. Available at: https://pdf.hres.ca/dpd_pm/00052036.PDF