Alaska ID ECHO: HCV-HIV-PrEP-STIs

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

NPAIHB
Indian Leadership for Indian Health

June 14, 2022

This program is supported by a grant from the Northwest Portland Area Indian Health Board and funding is provided from the HHS Secretary's Minority HIV/AIDS Fund.

Welcome to Alaska Infectious Disease ECHO: HCV, HIV, PrEP, STIs

Approved Provider Statements:

In support of improving patient care, Alaska Native Medical Center (ANMC) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Contact Hours:

ANMC designates this activity for a maximum of 12 contact hours, including 3 total pharmacotherapeutics contact hours, commensurate with participation.

Financial Disclosures:

Youssef Barbour, MD & Lisa Townshend-Bulson, APRN / faculty for this educational event, are primary investigators in an ANTHC sponsored hepatitis C study funded in part by Gilead Sciences. All of the relevant financial relationships listed have been mitigated.

Requirements for Successful Completion:

To receive CE credit please make sure you have actively engaged in the entire activity, your attendance is recorded by the facilitator, and complete the course evaluation form found here: https://forms.gle/18t4EgvN2WdnM4P77

For more information contact
jlfielder@anthc.org or (907) 729-1387

WELCOME

- Where are you joining from today?
- The recording of the didactic presentation will be available at, www.anthc.org/ak-id-echo with the presentation slides.
- Questions will be saved until the end of the didactic presentation. Feel free to put your questions in the chat for the Q&A.

Thank you for participating!

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

Drug Interactions:

Understanding “What” may happen and “How” to manage

Part II: Common drug interactions for medications commonly used to treat COVID-19

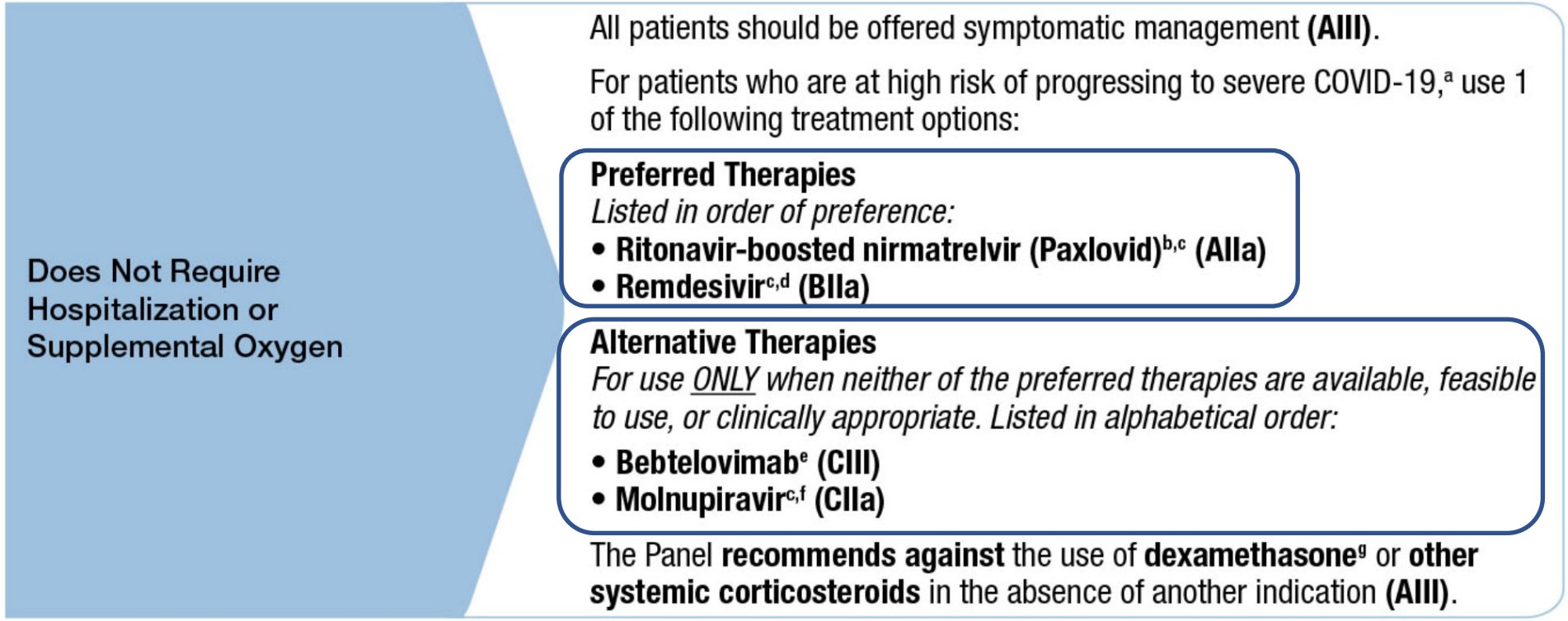
Rod Gordon, R.Ph. AAHIVP
RASU Staff Pharmacist
Anchorage, Alaska
June 14, 2022

NIH COVID-19 Treatment Guidelines

Clinical Management Summary

Last Updated: April 8, 2022

Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19



https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/clinical-management-summary/?utm_source=site&utm_medium=home&utm_campaign=highlights

Dexamethasone recommended when supplemental oxygen is required

Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[e]) **(CIIa)**.	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:[f] • **Therapeutic dose** of heparin[g] **(CIIa)** For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIIb)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the options above.[d,h]	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)** If patient is started on therapeutic heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Recommends against use of dexamethasone when supplemental oxygen not required

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/clinical-management-summary/?utm_source=site&utm_medium=home&utm_campaign=highlights

Nirmatrelvir/ritonavir and COVID

- Nirmatrelvir/ritonavir (Paxlovid®) is the most effective oral agent for the treatment of COVID in non-hospitalized patients.
  - 88-89% protective against disease progression, with no deaths in the treatment arm versus 13 with placebo (Hammond et al., *NEJM* 2022)
- Because the target for this drug, the coronavirus protease Mpro, is highly conserved, the drug is likely to retain activity against new variants of SARS-CoV-2, as well as SARS-CoV-1 and MERS.
- Because the Mpro target is essential and highly conserved, the drug appears to have a high barrier to resistance.

Nirmatrelvir/ritonavir and drug interactions

- Nirmatrelvir is a CYP 3A4 substrate and can be boosted by RTV and cobicistat, just like HIV protease inhibitors.
- Nirmatrelvir/ritonavir includes 100 mg of RTV given BID for 5 days.
- All of the drug interaction potential for nirmatrelvir/ritonavir is from the RTV component, BUT:
  - Keep in mind: Only given for 5 days!
  - Keep in mind: RTV inhibition of CYP 3A4 can persist for several days after the drug is stopped*
  - Keep in mind: RTV is also a P450 inducer!

* Washington CB, Flexner C, Sheiner LB, Rosenkranz SL, Segal Y, Aberg JA, Blaschke TF; AIDS Clinical Trials Group Protocol (ACTG 378) Study Team. Effect of simultaneous versus staggered dosing on pharmacokinetic interactions of protease inhibitors. Clin Pharmacol Ther. 2003 May;73(5):406-16. doi: 10.1016/s0009-9236(03)00006-7. PMID: 12732841.

Contraindications

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions *(see Drug Interactions (7.3)):*

- Alpha$_1$-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

} Sensitive CYP3A4 Substrates

PAXLOVID is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer *[see Drug Interactions (7.3)]:*

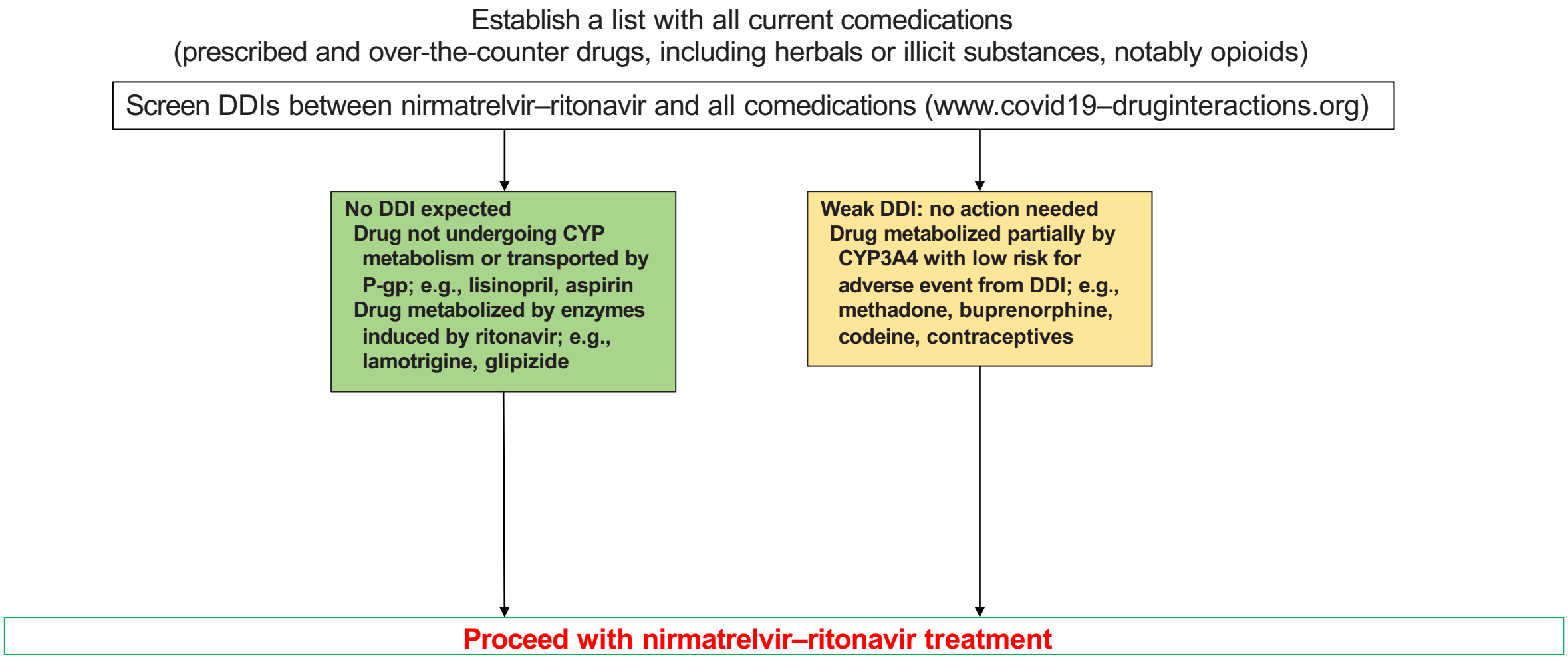
- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort *(hypericum perforatum)*

} Potent CYP3A4 Inducers

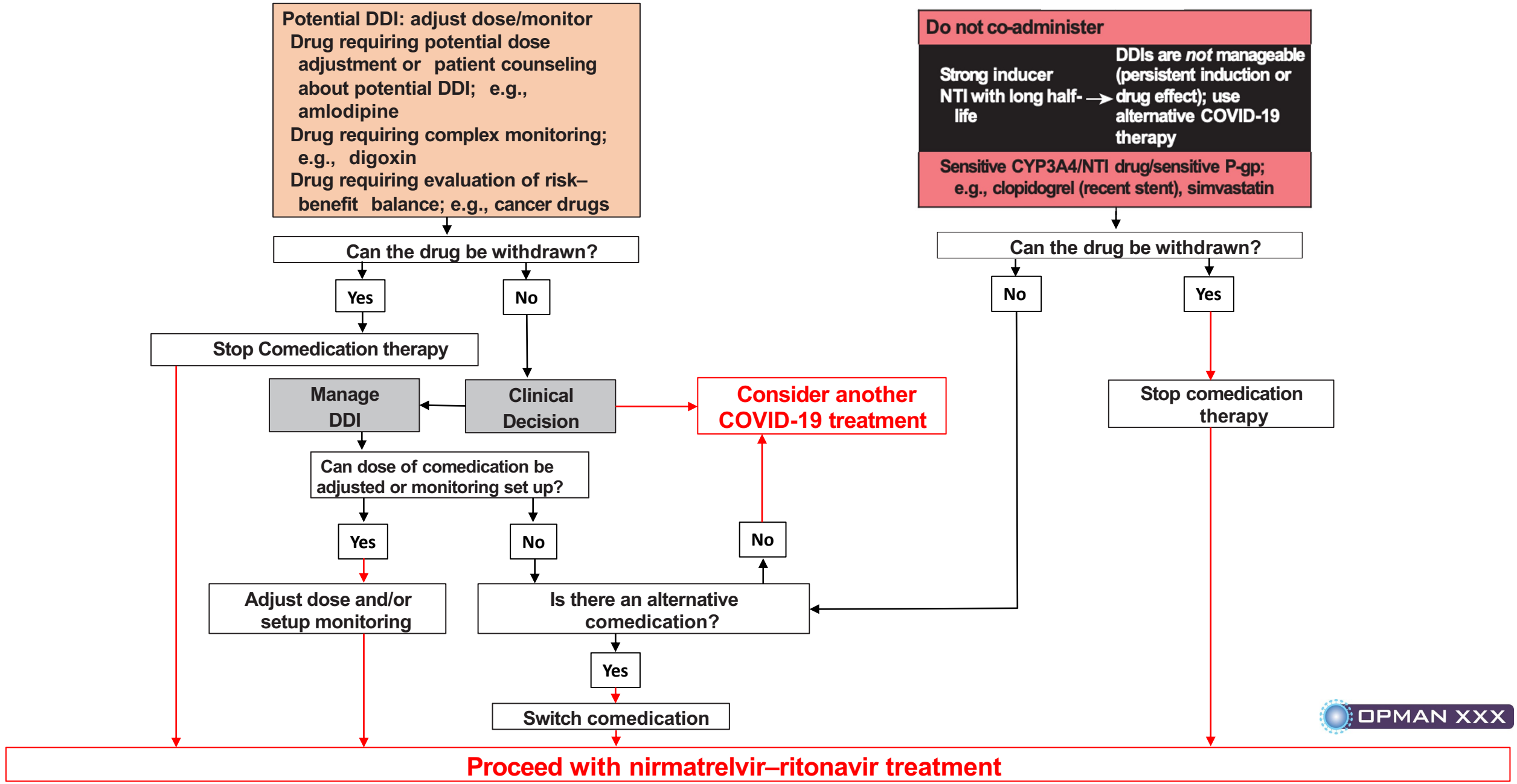
Prescribing Nirmatrelvir–Ritonavir: How to Recognize and Manage Drug–Drug Interactions

Catia Marzolini, PharmD, PhD; Daniel R. Kuritzkes, MD; Fiona Marra, PharmD; Alison Boyle, PharmD; Sara Gibbons, MPhil; Charles Flexner, MD; Anton Pozniak, MD; Marta Boffito, MD, PhD; Laura Waters, MD; David Burger, PharmD, PhD; David Back, PhD; and Saye Khoo, MD

Annals of Internal Medicine
March 1, 2022



Marzolini, C. et al. Prescribing Nirmatrelvir–Ritonavir: How to Recognize and Manage Drug–Drug Interactions. 2022, Annals of Internal Medicine, 744-746 (175-5), https://www.acpjournals.org/doi/abs/10.7326/M22-0281



The inhibitory effect of ritonavir takes several days to resolve. Thus, paused comedication therapy should be restarted 3 days after the last dose of nirmatrelvir–ritonavir. The same timeline applies for comedications whose dosage has been adjusted during nirmatrelvir–ritonavir treatment. CYP = cytochrome; DDI = drug–drug interaction; NTI = narrow therapeutic index; P-gp = P-glycoprotein.

Best Websites for COVID-19 Drug Interactions

1. COVID-19 Drug Interactions — University of Liverpool

https://www.covid19-druginteractions.org/

2. Updated: February 23, 2022

Nirmatrelvir/ Ritonavir (*Paxlovid*)

What Prescribers and Pharmacists Need to Know

Science Table — COVID-19 Advisory for Ontario

University of Waterloo | School of Pharmacy

https://covid19-sciencetable.ca/sciencebrief/nirmatrelvir-ritonavir-paxlovid-what-prescribers-and-pharmacists-need-to-know-2-0/

3. **Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians**

IDSA — Infectious Diseases Society of America

IDSA COVID-19 TREATMENT AND MANAGEMENT GUIDELINE PANEL ON BEHALF OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Last Updated: May 6, 2022- *Version 1.1**

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/management-of-drug-interactions-with-nirmatrelvirritonavir-paxlovid/

4. NIH | **COVID-19 Treatment Guidelines**

Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

Last Updated: May 13, 2022

Best Websites for HIV and General Drug Interactions

5. HIV Drug Interactions — University of Liverpool

https://www.hiv-druginteractions.org/checker

6. * Elsevier — Clinical Pharmacology powered by ClinicalKey®

https://www.clinicalkey.com/pharmacology/login

7. * IBM Micromedex® Drug Interactions

https://www.micromedexsolutions.com/home/dispatch

8. * Facts and Comparisons® Lexicomp®

https://fco.factsandcomparisons.com/lco/action/login

* Requires Subscription Fee

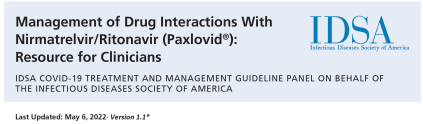
Paxlovid – Relapse/Retreatment?

*"….**Pfizer is unable to make any recommendations regarding re-treatment** in individual patients following a 5- day course of nirmatrelvir tablets; ritonavir tablets; **clinical judgment based on the medical history and the clinical status of a specific patient should dictate the appropriate actions to be taken**."*

Pfizer Medical Information

https://www.pfizermedicalinformation.com/en-us/document/a0r68000002xLHaAAM

*"….**If relapse occurs after initial treatment and a second course of treatment is warranted**, duration of therapy should be used to guide adjustments to concomitant medications."*


Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians

IDSA Infectious Diseases Society of America

IDSA COVID-19 TREATMENT AND MANAGEMENT GUIDELINE PANEL ON BEHALF OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Last Updated: May 6, 2022- *Version 1.1**

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/management-of-drug-interactions-with-nirmatrelvirritonavir-paxlovid/

*"….in communications with clinicians, the **FDA and Pfizer have made it clear that the people who relapse are in fact eligible for re-treatment under the Emergency Use Authorization (EUA)**. In other words, the **within-5-day symptom clock starts over with the relapse**. This would be justified clinically for our highest-risk patients (severely immunocompromised, medically fragile, or with severe recurrent symptoms), and favored over other outpatient treatments (all of which have logistical or efficacy issues) until we know more."*

HIV and ID Observations

An ongoing dialogue on HIV/AIDS, infectious diseases, all matters medical, and some not so medical.

MAY 4TH, 2022

Paul E. Sax, MD
Contributing Editor
NEJM JOURNAL WATCH INFECTIOUS DISEASES

More on Relapses after Paxlovid Treatment for COVID-19

https://blogs.jwatch.org/hiv-id-observations/index.php/more-on-relapses-after-paxlovid-treatment-for-covid-19/2022/05/04/

Case 1

- You are following a 57 y.o. woman with a H/O renal allograft transplantation. She was previously doing well on a regimen that included tacrolimus, 5 mg p.o. QD. She has been vaccinated against COVID, with her last mRNA booster in early November.
- She was recently exposed to COVID at a family reunion. She woke up 2 days after this exposure feeling feverish and reported to the emergency room, where she had a positive rapid test for SARS-CoV-2. She reports some myalgias but is not dyspneic, and her oxygen saturation on room air is 98%.
- Because she is immunocompromised, the ER physician caring for her wants to start a 5-day course of oral nirmatrelvir/ritonavir (Paxlovid®).
- You get a call from the ER because the prescribing physician wants to know what to do with her 5mg daily dose of tacrolimus while she is getting nirmatrelvir/ritonavir.

Paxlovid + Tacrolimus

COVID-19 Drug Interactions | University of Liverpool

Do Not Coadminister

Tacrolimus is metabolized by CYP3A4 and is a substrate of P-gp.

Coadministration with a ritonavir-boosted HIV protease inhibitor has been reported to profoundly increase tacrolimus concentrations which rapidly reach toxic levels.

Avoid use of nirmatrelvir/ritonavir unless close monitoring of immunosuppressant serum concentrations is feasible.

Considering the complex management of this interaction, an alternative COVID treatment will need to be considered.

However, if frequent therapeutic drug monitoring for tacrolimus is available, it has been suggested to withhold all tacrolimus doses during treatment with nirmatrelvir/ritonavir (days 1-5). If feasible, it would be advisable to measure tacrolimus concentrations on day 3 to assess the need for a one-time tacrolimus dose during nirmatrelvir/ritonavir treatment. Tacrolimus concentrations should be assessed on day 6 or 7 (and every 2-4 days thereafter) and concentrations used to guide the continued withholding or gradual reintroduction of tacrolimus.

Real-life observations in four transplant recipients in whom tacrolimus was held on the first day of nirmatrelvir/ritonavir treatment (day 1) suggest that tacrolimus should be reintroduced between days 8 and 10 depending on tacrolimus drug levels.

Caution Urged With Paxlovid in Transplant Patients

— Small case series emphasizes the need to discontinue tacrolimus prior to starting therapy

by Molly Walker, Deputy Managing Editor, MedPage Today May 13, 2022

> "Based on their experience, Lee's team recommended holding tacrolimus during the 5-day course of nirmatrelvir/ritonavir (or even 1 to 2 days prior to starting the antiviral for high-risk patients), checking tacrolimus concentrations on days 2 to 3 of therapy, and bi-weekly drug monitoring following reinitiation of tacrolimus."

Case 1

What should you recommend to the ER physician?

- Plan to hold tacrolimus for the 5-day duration of Paxlovid treatment, and delay starting Paxlovid by 1 day, if possible, to lower the pretreatment tacrolimus AUC.
- Plan to closely monitor tacrolimus drug levels.
- Measure tacrolimus serum concentrations on day 2 or 3 of Paxlovid treatment to assess the need for a one-time tacrolimus dose.
- Measure tacrolimus concentrations again on day 6 or 7 (and every 2-4 days thereafter).
- Use concentrations to guide the continued withholding or gradual reintroduction of tacrolimus.

Case 2

- You are involved in the care of a 62 y.o. woman with a long h/o HIV infection. She has done well on daily oral ARVs but switched to monthly long-acting cabotegravir and rilpivirine (Cabenuva®) 4 months ago because of pill fatigue.
- She has a history of well controlled COPD but never received the SARS-CoV-2 vaccine because she is vaccine hesitant. She was recently diagnosed with COVID-19 and started on Paxlovid 2 days ago [day 5 after onset of symptoms] by her PCP to prevent disease progression.
- Despite Paxlovid treatment she presents to the ER today with significant SOB and an O_2 Sat of 89%. The ER physician immediately starts O_2 supplementation by nasal cannula and plans to add dexamethasone, 6mg PO per day, to help manage the inflammatory response to COVID.
- You are called by the ER because the hospital's EHR flagged the co-administration of dexamethasone and cabotegravir/rilpivirine as being contraindicated. It also recommended to avoid the co-administration of dexamethasone and Paxlovid.
- What should you recommend to the ER physician?

Cabenuva + Dexamethasone*

HIV Drug Interactions | University of Liverpool

Dexamethasone

Quality of evidence: Very Low

Summary:

Coadministration is contraindicated with systemic dexamethasone (except as a single dose) as significant decreases in rilpivirine plasma concentrations may occur.

Do Not Coadminister

Dexamethasone is a dose dependent CYP3A4 inducer and may decrease rilpivirine concentrations due to induction of CYP3A4.

No significant effect is expected on cabotegravir as indicated by a drug-drug interaction study with rifabutin (a moderate inducer).

In the specific case of patients being treated with short term dexamethasone for COVID-19 please refer to www.covid19-druginteractions.org for additional advice

Coadministration is predicted to decrease concentrations of rilpivirine. Coadministration is contraindicated with Cabenuva due to potential for loss of virologic response and development of resistance. *Cabenuva (cabotegravir/rilpivirine extended-release injection) US Prescribing Information, ViiV Healthcare, January 2021.*

Paxlovid + Dexamethasone

COVID-19 Drug Interactions | UNIVERSITY OF LIVERPOOL

No Interaction Expected

Dexamethasone (low dose)

Quality of Evidence: Very Low

Summary:

Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.

Dexamethasone is a weak CYP3A4 inducer at a low dose and is unlikely to have a clinically significant effect on nirmatrelvir/ritonavir.

Product labels for dexamethasone do not recommend coadministration of strong CYP3A4 inhibitors with dexamethasone due to the risk of Cushing's syndrome but based on the low dose of dexamethasone used in COVID-19 treatment and given the short duration of nirmatrelvir/ritonavir treatment, this risk is considered to be low.

A retrospective review of published case reports of individuals developing a Cushing's syndrome while treated concurrently with a boosted HIV protease inhibitor and inhaled corticosteroids indicated that this adverse effect tended to occur after several months (and more rarely 2 weeks) of concurrent administration of these drugs.

Updated: February 23, 2022

Nirmatrelvir/ Ritonavir (*Paxlovid*)

What Prescribers and Pharmacists Need to Know

SCIENCE TABLE
COVID-19 ADVISORY FOR ONTARIO

UNIVERSITY OF WATERLOO | SCHOOL OF PHARMACY

Paxlovid + Dexamethasone

High dose (20 mg daily): Reduce dexamethasone dose by 50% and resume usual dose 2 days after completing nirmatrelvir/ritonavir.

Low dose (<20 mg daily): Continue with usual dose during nirmatrelvir/ritonavir.

Dexamethasone AUC increased almost 3-fold when coadministered with voriconazole.
Li M, Zhu L, Chen L et al. Assessment of drug-drug interactions between voriconazole and glucocorticoids. J Chemother. 2018;30(5):296-303. doi: 10.1080/1120009X.2018.1506693.

Potential for risk of dexamethasone toxicity with high doses (20 mg daily).

Clinically significant interaction is not expected with dexamethasone at low doses, including when used for COVID-19 treatment.

Dexamethasone as an inducer in humans

- Dexamethasone modestly induces CYP 3A4 (by 25-30%) when given at high doses (16-24 mg/day) for up 9 days, as indicated by the ^{14}C-erythromycin breath test. The mechanism for this effect is not clear, but it is mainly seen in those with low baseline CYP 3A4 activity.
- Low doses of dexamethasone do not alter the concentrations of co-administered triazolam, a CYP 3A4 substrate, (1.5 mg/day for 4 days).
- Very high-dose dexamethasone (40 mg/day on days 1-4 and 9-12 during lymphoma treatment) had no effect on concentrations of bortezomib, which is a CYP 3A4 substrate.
- The balance of data suggest that dexamethasone is unlikely to be a clinically significant CYP inducer in humans.

Al Rihani SB, Deodhar M, Dow P, Turgeon J, Michaud V. Is Dexamethasone a Substrate, an Inducer, or a Substrate-Inducer of CYP3As? Arch Phar & Pharmacol Res. 2(5): 2020. APPR.MS.ID.000546. https://irispublishers.com/appr/fulltext/Is-Dexamethasone-a-Substrate,-an-Inducer.ID.000546.php

Case 2

What should you recommend to the ER physician?

- Disregard the EHR alerts for both potential drug interactions
- Neither potential drug interaction is expected to be clinically significant
- Low dose/short term dexamethasone is not contraindicated with Cabenuva
- No significant interaction between low dose dexamethasone and Paxlovid is expected

Case 3

- You are involved in the care of a 62 y.o. woman with a long h/o HIV infection. She has been well controlled on Genvoya [elvitegravir/cobicistat + tenofovir AF + emtricitabine]
- In addition to HIV, she has a history of HTN, and HLD.
- Her medications include Genvoya 1 tablet daily, amlodipine 10mg daily, rosuvastatin 10mg daily.
- She has never received the SARS-CoV-2 vaccine because she is vaccine hesitant.
- She recently attended a birthday party for a grandchild and now, 3 days later, has dyspnea, fever, cough and fatigue. She goes to the ER where she tests positive for COVID-19. The ER physician wants to immediately start Paxlovid.
- You get an urgent call from the ER provider because the hospital's EHR flags a potential DDI between Paxlovid and Genvoya, Paxlovid and amlodipine, and between Paxlovid and rosuvastatin.
- What should you recommend to the ER physician?

Paxlovid + Genvoya

COVID-19 Drug Interactions | University of Liverpool

Quality of Evidence: Very Low

Summary:
Coadministration has not been studied.

Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment with no dosage modification.

Potential Interaction

No interaction is expected with emtricitabine.

Tenofovir alafenamide (the prodrug of tenofovir) is a substrate of P-gp and ritonavir, a P-gp inhibitor, is expected to increase the absorption of tenofovir alafenamide, thereby increasing the systemic concentration of tenofovir.

However, this increase is not problematic as tenofovir alafenamide has a good safety profile. No dose adjustment is required.

Paxlovid + Amlodipine

COVID-19 Drug Interactions | UNIVERSITY OF LIVERPOOL

Potential Interaction

Quality of Evidence: Very Low

Summary:

Coadministration has not been studied.

Amlodipine is metabolized by CYP3A4. Nirmatrelvir/ritonavir is predicted to increase amlodipine exposure by ~2-fold based on drug-drug interactions studies with amlodipine and indinavir/ritonavir or paritaprevir/ritonavir leading to the recommendation to reduce amlodipine dosage by 50%.

However, a dose adjustment can be optional in the case of amlodipine, given that patients can be advised to monitor for symptoms of hypotension and to temporarily pause the antihypertensive drug if needed.

The inhibitory effect of ritonavir is expected to last up to 3 days after the last administered dose of nirmatrelvir/ritonavir.

Paxlovid + Rosuvastatin

COVID-19 Drug Interactions | University of Liverpool

Quality of Evidence: Very Low

Summary:

Coadministration with nirmatrelvir/ritonavir has not been studied. Rosuvastatin is largely excreted unchanged via the feces. Based on data with a boosted PI (lopinavir/ritonavir), a dose modification of rosuvastatin may be required. This is due to inhibition of drug transporters by ritonavir.

Potential Interaction

Given the short duration nirmatrelvir/ritonavir treatment, rosuvastatin should be stopped. The pragmatic approach to stop temporarily rosuvastatin (or any other statin) is acceptable considering that it will not negatively affect the therapeutic effect but can minimize the risk for adverse events related to a drug interaction.

If coadministration is necessary, do not exceed 10 mg rosuvastatin per day.

Case 3

What should you recommend to the ER physician?

- Continue the patient's HIV regimen, using Genvoya without any dosage adjustment and recommend monitoring for increased GI side effects… possibly diarrhea and nausea during Paxlovid treatment period.
- Reduce amlodipine dose by 50% [1/2 tablet] for the 5 days of Paxlovid Tx and an additional 3 days afterward, then resume amlodipine.
- Hold rosuvastatin for the 5 days of Paxlovid Tx and for an additional 3 days afterward, then resume rosuvastatin.

Paxlovid and other potential DDIs/FAQs?

◆ Alprazolam (*Xanax*)

COVID-19 Drug Interactions | University of Liverpool

Potential Interaction

Hold and restart 2 days after completing nirmatrelvir/ritonavir.

Alternatively, reduce alprazolam dose by at least 50% and monitor for increased effects.

Alprazolam AUC increased 148% and half-life increased from 13 to 30 hours when coadministered with ritonavir 200 mg x 4 doses.

◆ Buspirone (*Buspar*)

COVID-19 Drug Interactions | University of Liverpool

Potential Interaction

Hold and restart 2 days after completing nirmatrelvir/ritonavir.

Alternatively, reduce buspirone dose to 2.5 mg daily if the usual dose is 20 to 30 mg/day.

Buspirone AUC increased 19-fold when coadministered with itraconazole 200 mg/day for 4 days.

● Clonazepam

COVID-19 Drug Interactions | University of Liverpool

Do Not Coadminister

Hold and restart 2 days after completing nirmatrelvir/ritonavir.

If an anxiolytic is needed, use lorazepam, oxazepam, or temazepam at usual doses.

Due to prolonged benzodiazepine half-life, coadministration is not recommended.

Paxlovid - and other potential DDIs/FAQs?

Paxlovid for the Treatment of COVID-19:
Considerations for People With HIV and Hepatitis C
Version: 5/9/2022

Can people with HIV develop drug resistance to protease inhibitors with Paxlovid?

• While people with undiagnosed or uncontrolled HIV could theoretically develop protease inhibitor resistance, given the short duration of Paxlovid therapy (5 days), this is very unlikely.

Are dosing adjustments recommended when co-administering Paxlovid with other therapies containing ritonavir or cobicistat?

• A dosage adjustment is not required when treating patients with Paxlovid who are taking HIV or HCV regiments containing ritonavir or cobicistat.

Paxlovid for the Treatment of COVID-19: Considerations for People with HIV and Hepatitis C Version: 5-9-2022. https://www.idsociety.org/globalassets/covid-19-real-time-learning-network/patient-populations/hiv/oral-covid-tx-considerations-for-people-with-hiv-and-hcv.pdf

References

National Institute of Health COVID Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/clinical-management-summary/?utm_source=site&utm_medium=home&utm_campaign=highlights
Accessed: May 28, 2022

Marzolini, C. et al. Prescribing Nirmatrelvir–Ritonavir: How to Recognize and Manage Drug–Drug Interactions. 2022, Annals of Internal Medicine, 744-746 (175-5), https://www.acpjournals.org/doi/abs/10.7326/M22-0281

Lee B, Rose D. Rifampin reversal for tacrolimus toxicity. Oxford University Press on behalf of Infectious Diseases Society of America and HIV Medicine Association. This is an Open Access article distributed under the terms of the Creative Commons Attribution: Non-Commercial-NoDerivs license (https://creativecommons.org/licenses/by-nc-nd/4.0/)

Washington CB, Flexner C, Sheiner LB, Rosenkranz SL, Segal Y, Aberg JA, Blaschke TF; AIDS Clinical Trials Group Protocol (ACTG 378) Study Team. Effect of simultaneous versus staggered dosing on pharmacokinetic interactions of protease inhibitors. Clin Pharmacol Ther. 2003 May;73(5):406-16. doi: 10.1016/s0009-9236(03)00006-7. PMID: 12732841.

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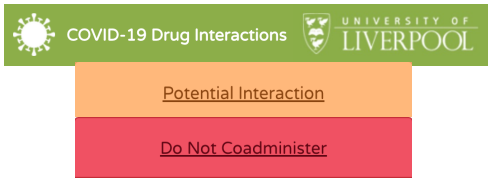
Paxlovid for the Treatment of COVID-19: Considerations for People with HIV and Hepatitis C Version: 5-9-2022. https://www.idsociety.org/globalassets/covid-19-real-time-learning-network/patient-populations/hiv/oral-covid-tx-considerations-for-people-with-hiv-and-hcv.pdf

Paxlovid - and other potential DDIs/FAQs?

- Clopidogrel (*Plavix*)

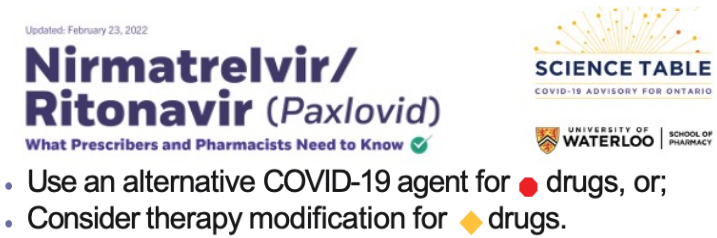


Acute coronary syndrome (ACS)/percutaneous coronary intervention (PCI):

- **If <1 month since ACS:** Use alternative COVID-19 agent.
- **If <3 months since ACS or <1 month since PCI (no ACS):** Consider switching clopidogrel to prasugrel (if age <75, weight >60 kg, and no history of stroke/TIA) and resume clopidogrel 2 days after completing nirmatrelvir/ritonavir;
- **If >3 months since ACS or >1 month since PCI (no ACS):** Continue clopidogrel with acetylsalicylic acid (ASA) during nirmatrelvir/ritonavir therapy. If not taking ASA, consider switching to prasugrel (if age <75, weight >60 kg, and no history of stroke/TIA) and resume clopidogrel 2 days after completing nirmatrelvir/ritonavir.

Coadministration will decrease the antiplatelet effect of clopidogrel.

Clopidogrel active metabolite AUC decreased by 51 to 69% when coadministered with ritonavir.



Paxlovid - and other potential DDIs/FAQs?

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Clopidogrel	↓	Increased clotting	• Avoid nirmatrelvir/ritonavir for 6 weeks after coronary stenting • Other patients: No change

Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians

IDSA Infectious Diseases Society of America

IDSA COVID-19 TREATMENT AND MANAGEMENT GUIDELINE PANEL ON BEHALF OF THE INFECTIOUS DISEASES SOCIETY OF AMERICA

Last Updated: May 6, 2022- *Version 1.1**

Paxlovid - and other potential DDIs/FAQs?

- Colchicine in renal/ hepatic Impairment

Coadministration is contraindicated in patients with renal and/or hepatic impairment.

In patients with **normal renal/hepatic function,** colchicine may be administered at a lowered dose if practical:

- **Treatment of gout flares:** 0.6 mg x 1 dose, then 0.3 mg (½ tablet) 1 hour later. Repeat dose no earlier than 3 days.
- **Prevention of gout flares:**
  a) If originally on 0.6 mg twice daily: decrease to 0.3 mg once daily;
  b) If originally on 0.3 mg twice daily, decrease to 0.3 mg once every 2 days.
- **Treatment of Familial Mediterranean fever:** maximum 0.6 mg (or 0.3 mg twice daily).

In all cases, resume usual colchicine dose 2 days after completing nirmatrelvir/ritonavir.

Drug interaction could lead to potentially life-threatening/fatal adverse events.

Updated: February 23, 2022

Nirmatrelvir/ Ritonavir (*Paxlovid*)

What Prescribers and Pharmacists Need to Know

SCIENCE TABLE
COVID-19 ADVISORY FOR ONTARIO

UNIVERSITY OF WATERLOO | SCHOOL OF PHARMACY

- Use an alternative COVID-19 agent for ● drugs, or;
- Consider therapy modification for ◆ drugs.

Paxlovid - and other potential DDIs/FAQs?

◆ Diltiazem (*Cardizem*) COVID-19 Drug Interactions · University of Liverpool Potential Interaction	**Reduce diltiazem dose by 50%** and restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor heart rate and blood pressure.	Concentrations of calcium channel blockers are expected to increase when coadministered with nirmatrelvir/ritonavir.
◆ Verapamil COVID-19 Drug Interactions · University of Liverpool Potential Interaction	**Reduce verapamil dose by 50%** and restart usual dose 2 days after completing nirmatrelvir/ritonavir. Monitor blood pressure.	Concentrations of calcium channel blockers are expected to increase when coadministered with nirmatrelvir/ritonavir.

Updated: February 23, 2022

Nirmatrelvir/ Ritonavir (*Paxlovid*)

What Prescribers and Pharmacists Need to Know

SCIENCE TABLE
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University of Waterloo | School of Pharmacy

- Use an alternative COVID-19 agent for ● drugs, or;
- Consider therapy modification for ◆ drugs.

Paxlovid - and other potential DDIs/FAQs?

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Calcium-channel blockers (diltiazem, verapamil)	↑	Decreased blood pressure	• Continue if tolerated • Reduce dose if patient has low blood pressure or bradycardia

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Paxlovid - and other potential DDIs/FAQs?

- Apixaban (*Eliquis*)

If possible, use alternative COVID-19 agent. If not possible, ensure stable renal function, then in:

Acute venous thromboembolism (VTE):
Hold apixaban and restart 2 days after completing nirmatrelvir/ritonavir. While apixaban is on hold, start therapeutic dosing of a subcutaneous low molecular weight heparin (LMWH) such as:

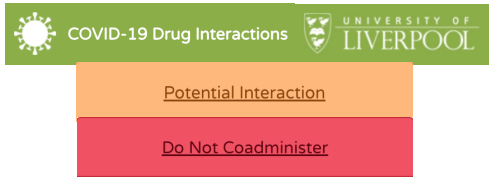
- Dalteparin 200 units/kg daily OR 100 units/kg every 12 hours if >90 kg;
- Enoxaparin 1 mg/kg every 12 hours (preferred) or 1.5 mg/kg once every 24 hours;
- Tinzaparin 175 anti-Xa units/kg once daily.

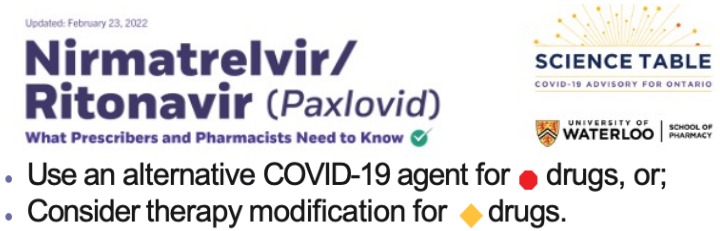
Atrial fibrillation:
Decrease apixaban to 2.5 mg twice daily, then resume usual dose 2 days after completing nirmatrelvir/ritonavir.

If patient is taking 2.5 mg twice daily, use an alternative COVID-19 agent.

Canadian monograph states that coadministration with ritonavir is contraindicated. However, US product monograph suggests to decrease 5 mg twice daily dose to 2.5 mg twice daily when combined with strong inhibitors of CYP3A4 and P-glycoprotein.

Eliquis (U.S.) Prescribing Information. Accessed February 8, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/2 02155s000lbl.pdf





Paxlovid - and other potential DDIs/FAQs?

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Apixaban	↑	Increased bleeding	Dose dependent: • Apixaban 2.5 mg: Avoid nirmatrelvir/ ritonavir • Apixaban 5mg or 10 mg: Reduce dose by 50% until 3 days after nirmatrelvir/ritonavir

Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians

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Paxlovid - and other potential DDIs/FAQs?

- Rivaroxaban (*Xarelto*)

COVID-19 Drug Interactions | University of Liverpool

Do Not Coadminister

If possible, use alternative COVID-19 agent. If not possible, then:

Acute venous thromboembolism (VTE):
Hold and restart 2 days after completing nirmatrelvir/ritonavir. While rivaroxaban is on hold, start therapeutic dosing of a subcutaneous low molecular weight heparin (LMWH) such as:

- Dalteparin 200 units/kg daily OR 100 units/kg every 12 hours if >90 kg;
- Enoxaparin 1 mg/kg every 12 hours (preferred) or 1.5 mg/kg once every 24 hours;
- Tinzaparin 175 anti-Xa units/kg once daily.

Atrial fibrillation:
Use an alternative COVID-19 agent.

Rivaroxaban AUC and Cmax increased by 153% and 55%, respectively, when coadministered with ritonavir 600 mg twice daily in healthy volunteers.

Observational data from Italy found a 600 to 3000% increase in rivaroxaban levels in combination with *antivirals* containing ritonavir in hospitalized patients.

Testa S, Prandoni P, Paoletti O et al. Direct oral anticoagulant plasma levels' striking increase in severe COVID-19 respiratory syndrome patients treated with antiviral agents: The Cremona experience. *J Thromb Haemost.* 2020;18:1320–1323. https://doi.org/10.1111/jth.14871

Updated: February 23, 2022

Nirmatrelvir/ Ritonavir (Paxlovid)

What Prescribers and Pharmacists Need to Know

SCIENCE TABLE
COVID-19 ADVISORY FOR ONTARIO

University of Waterloo | School of Pharmacy

- Use an alternative COVID-19 agent for ● drugs, or;
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Paxlovid - and other potential DDIs/FAQs?

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Rivaroxaban	↑	Increased bleeding	Avoid nirmatrelvir/ritonavir

Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians

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Paxlovid - and other potential DDIs/FAQs?

- Hydrocodone

COVID-19 Drug Interactions | University of Liverpool

Potential Interaction

Reduce dose by about 50% or switch to equivalent dose of hydromorphone:

- Multiply hydrocodone dose by 0.25 to get equivalent hydromorphone dose.
- Consider further reducing hydromorphone dose by 25 to 50% to account for cross tolerance.

Monitor for signs of opioid toxicity. **Resume usual hydrocodone dose 2 days after completing nirmatrelvir/ritonavir.**

Hydrocodone is metabolized to active metabolites: hydromorphone and norhydrocodone.

Hydrocodone AUC increased by 90% when coadministered with ritonavir/ombitasvir/ paritaprevir combination.

- Oxycodone (*Percocet*)

COVID-19 Drug Interactions | University of Liverpool

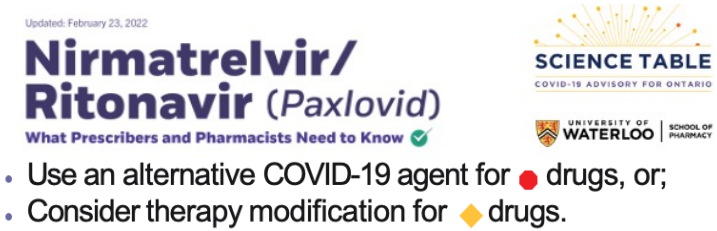
Potential Interaction

Reduce dose of oxycodone by 66% or switch to equivalent dose of hydromorphone:

- Multiply oxycodone dose by 0.3 to get equivalent hydromorphone dose.
- Consider further reducing hydromorphone dose by 25 to 50% to account for cross tolerance.

Monitor for signs of opioid toxicity. **Resume usual oxycodone dose 2 days after completing nirmatrelvir/ritonavir.**

Oxycodone half-life increased 2-fold and AUC increased between 3 and 4-fold when coadministered with other potent 3A4 inhibitors (i.e., voriconazole).



Paxlovid - and other potential DDIs/FAQs?

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Hydrocodone Oxycodone (with or without acetaminophen)	↑	Increased opioid side effects, sedation	Consider reducing frequency of dosing or reduced dose of hydrocodone/oxycodone

Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians

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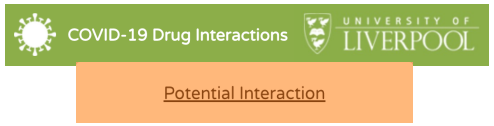
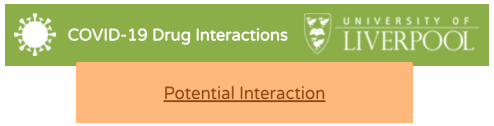
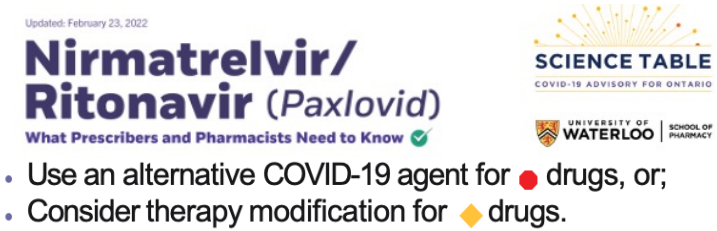
Paxlovid - and other potential DDIs/FAQs?

◆ Tramadol 	**Reduce tramadol dose by 50%** and monitor for pain relief and opioid toxicity. **Resume usual dose 2 days after** completing nirmatrelvir/ritonavir.	Inhibition of CYP3A4 may increase tramadol concentrations. Inhibition of CYP2D6 can decrease conversion of tramadol to a more active metabolite, but this is not expected to be significant when coadministered with nirmatrelvir/ritonavir.
◆ Zolpidem (*Ambien*) 	**Hold and restart 2 days after** completing nirmatrelvir/ritonavir. **If coadministration required, reduce zolpidem dose by 50%.**	Zolpidem AUC increased 70% when coadministered with ketoconazole.



Paxlovid - and other potential DDIs/FAQs?

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Tramadol	↓	Decreased effects, increased side effects	No dose adjustment required

Management of Drug Interactions With Nirmatrelvir/Ritonavir (Paxlovid®): Resource for Clinicians

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What questions do you have?

Please share questions in the chat or unmute yourself.

ALASKA NATIVE
TRIBAL HEALTH
CONSORTIUM

AK ID ECHO DIDACTIC TOPICS FOR 2022

- July 12: Public Health Reporting – procedures, processes and follow-up
- August 9: HCV Reinfection vs Treatment Failure
- September 13: Hepatitis B Screening and Lab Interpretation
- October 11: Drug Interaction Considerations with Gender Affirming Hormone Therapy
- November 8: STI EPI Update
- December 13: HIV Update

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

ADDITIONAL LEARNING OPPORTUNITIES

Alaska Liver Disease ECHO

- Third Thursday of every month from 12:00-1:00 PM AKDT
- June 16: AIH in AN/AI Population in Alaska

www.anthc.org/project-echo/alaska-liver-disease-echo

LiverConnect

- Second Tuesday of every month 8:00-9:00 AM AKDT
- July 12: Alcohol Hepatitis Diagnosis, Evaluation for Treatment, Prognosis and Follow Up

www.anthc.org/hep/liverconnect

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

ADDITIONAL LEARNING OPPORTUNITIES

Addiction Medicine ECHO

- Second and fourth Thursday of every month from 12:00-1:00 PM

www.anthc.org/project-echo/addiction-medicine-echo

Indian Country ECHO Programs

- Harm Reduction, Infectious Disease, and more!

www.indiancountryecho.org/teleecho-programs

ALASKA NATIVE TRIBAL HEALTH CONSORTIUM

AK ID ECHO Contacts

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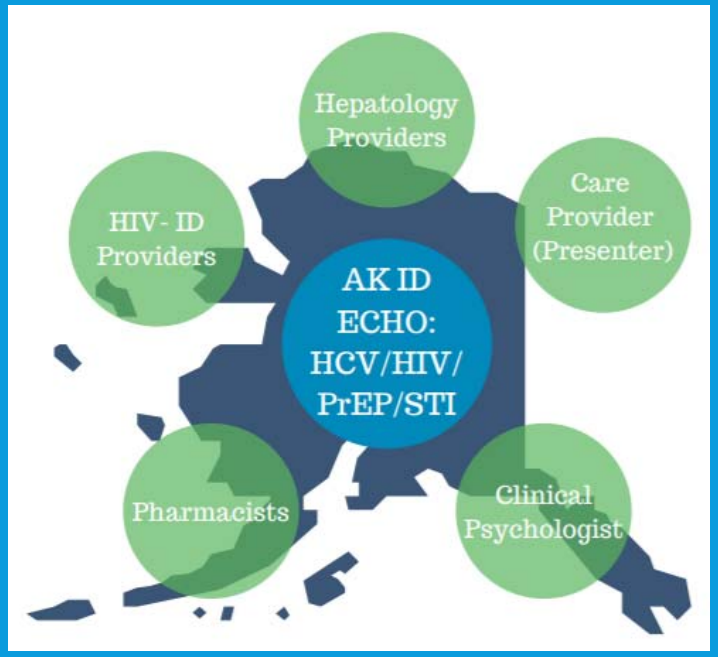
NPAIHB
Indian Leadership for Indian Health

Thank you!

AK ID ECHO is supported by a grant from the Northwest Portland Area Indian Health Board and funding is provided from the HHS Secretary's Minority HIV/AIDS Fund.

AK ID ECHO: CONSULTANT TEAM



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- Terri Bramel, PA-C HIV/STI Provider
- Rod Gordon, R.Ph. AAHIVP Pharmacist
- Jacob Gray, MD Infectious Disease Provider
- Annette Hewitt, ANP Hepatology Provider
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