CASES: Lessons Learned, Mysteries to Solve

Fourteenth Annual HIV Pharmacy Education Day – June 10, 2022

Introduction

Linda Robinson opened the virtual education day by thanking her HIV Pharmacy Education Day co-planners: Alice Tseng, Deborah Yoong, Pierre Giguere, and Sue Gill. She also thanked the case presenters for speaking, Ontario HIV Treatment Network staff members Tanya Producer and Diana Campbell for their technological support during the event, and Denise Kreutzwiser for taking minutes.

Linda recognized the sponsors of this education day and thanked them for making this day possible. Sponsors included: Ministry of Long-Term Care, AIDS Bureau, Ontario HIV Treatment Network, Gilead, Viiv Healthcare, Merck, Abbvie, and Pfizer. Messages of congratulations and appreciation for the work pharmacists do in caring for individuals living with HIV were provided by the following individuals:

- Kevin Schultz, Senior Director Sales and Marketing, Gilead Canada
- Dacia Hibbert, General Manager, Canada, Viiv Healthcare
- Drew Ferguson, Specialty Sales Representative, Virology, Merck
- Lyyne Jamme, Specialty Representative, Abbvie Canada

A land acknowledgement was also done, with recognition that attendees were joining this session from across the province of Ontario.

Lessons Learned

Case #1: Infection on PrEP: Follow-up

Sherri Livingston in Windsor, ON

Summary of case details presented in April 2021:

- 38 y.o. MSM on PrEP with TDF/FTC and reportedly adherent
- Oct. 2020 non-reactive HIV 1/2 Ag/Ab screen
- Feb. 2021 HIV 1/2 Ag/Ab screen reactive and suggestive of recent seroconversion, however also in Feb., HIV viral load (VL) testing came back target not detected (TND), CD4 = 1023
- Was taking daily PrEP until near end of Feb., off therapy HIV VL = 131 c/mL in early March.
- Able to genotype HIV VL of 140 c/mL in early March, started on BIC /TAF/FTC (Biktary) in mid-March, DOR added when genotype returned as patient's virus showed M184V, T215E and T66I mutations.
- Several questions existed as to while the HIV VL was so low at time of diagnosis, with one explanation being patient was suspected to be an elite controller.

Updates over the past year:

- Patient's HIV VL undetectable ever since starting BIC/TAF/FTC + DOR. Clinicians considered dropping DOR, but opted to continue it.
- Patient reflected on his history and believed he identified the source for his HIV infection; patient reported his suspected source to the public health unit and legal authorities and told his HIV clinicians.

- Suspected source was already a patient at the same HIV clinic, so clinicians looked at the suspected source's HIV VL, treatment and genotype history to see if any further insight could be obtained on whether or not to drop DOR from the patient's regimen. Suspected source's history:
    - Dx October 2018 with baseline HIV VL = 235K, started on TAF/FTC/EVG/COBI (Genvoya),
    - HIV VL = 59 c/mL in January 2019; HIV VL = 56 c/mL in December 2019
    - HIV VL = 3,167 c/mL in October 2020
    - HIV VL = 13K in February 2021; changed to DRV/COBI + DOR when genotype returns showing K70QTW, M184V, T215E, T66I, D2320N mutations
- Patient's genotype from the 140 c/mL HIV VL sample had shown 3/5 of the mutations as what the suspected source's genotype had. Did only 3 of the mutations show up because the HIV VL was so low? Patient was kept on TAF/FTC/BIK + DOR.
    - Discussion included how consideration could be given to switching to injectable cabotegravir/rilpivirine (Cabenuva) www.ncbi.nlm.nih.gov/pmc/articles/PMC5956922/
- November 2021 – public health contacted pharmacy asking for suspected source's medication dispensing history, which provoked a question - can this be released and what are the legal requirements here? Sheri had never had a request for such info before from public health, so reached out to her clinic and department management teams, as well as the hospital lawyer to get advice on what to do. In the end the dispensing record was not shared with public health as the patient didn't consent to the sharing of the information.
    - Resources for dealing with legal issues around the sharing of health information include:
        - PHIPA (Personal Health Information and Privacy Act) 2004
        - HALCO (www.halco.org)
        - (OCP) Ontario College of Pharmacists
- This case serves as a reminder that U=U and if someone stops ARVs that HIV transmission can happen and there can be ramifications involving public health and the authorities.

Case #2: Tough Resistance: Follow-up

Alissa Koop in Hamilton, ON

Summary of case details presented in April 2021:

- 58 y.o man with HIV diagnosis in 1992. Baseline CD4: 380 cells/mm^3. Marked decline in CD4+ in mid 90s, which dual/triple therapy reversed. Decline in HIV VL from Feb 1997 to May 1999 after that a steady increase in VL to May 2000.
- *Multiple comorbidities:*
    - lipoatrophy/lipodystrophy, hypertriglyceridemia, GERD, osteoporosis, hypertension
- *Non-ART Medications:*
    - Atovoquone 1500 mg daily, amlodipine 5 mg daily, omeprazole 20 mg daily, atorvastatin 10mg daily, alendronate 70mg weekly.
- *Allergies:*
    - Septra (rash), dapsone (rash)
- Complex ARV history:
    - Feb 1992- Nov 1994 – AZT
    - Nov 1994-May 1996 – AZT, ddC
    - May 1996-August 1996 – AZT, 3TC
    - Aug 1996-May 1997 – AST, 3TC, SQV
    - May 1997- Feb 1999 - d4T, 3TC, IDV

- Feb 1999-Feb 2000 – d4T, 3TC, NFV, EFV
- Feb 2000 - Aug 2000 - ABC, 3TC, SQV/RTV.
    - First genotype in May 2000 – showed high-level resistance to pretty much everything available. All ARVs stopped after receipt of May 2000 genotype.
- Sept. 2000 – June 2001 - d4T + ddI + EFV
- June 2001 to Aug 2004 - d4T, ABC, 3TC, LPV/RTV – VL suppressed (1000-3000 copies), CD4+ rose
    - In Aug 2002, T-20 added to regimen – lower VL but still some low-level viremia
    - Continued on this regimen to 2004 when breakthrough began; genotype done in 2004 – added new resistance mutations, showed intermediate resistance to some emerging agents
- Fall 2004: ABC + 3TC switched to TDF + EFV (LPV/RTV + T20 continues)
    - HIV VL reaches 4,500 copies/mL in 2007 (patient admitted only taking T-20 once daily (rather than twice daily)
- May 2007 switched to TDF, DRV/RTV BID, ETR BID and T20; undetectable HIV VL until Apr 2008 when broke through
    - 2008 genotype showed high-level resistance to all available agents (no integrase available)
- Nov. 2008, RAL added to TDF, DRV/RTV, ETR
    - HIV VL broke through in Aug. 2009
    - Patient was missing evening ARV doses; ARV regimen changed to once daily Jan. 2011
    - TDF changed to Q48H then stopped in May 2012 due to elevated creatinine
- May 2013 – RAL switched to DTG BID + DRV/RTV + ETR, VL increasing
- Feb 2014 put on TPV/RTV + DTG + ETR had a large viral spike
- May 2014 all meds stopped, no real options
- Aug to Nov. 2014 put on 3TC, DTG BID as viral fitness approach
- Dec. 2014 – Nov. 2019 put back on mega-HAART: TDF/FTC + DRV 600mg/RTV 100mg BID + ETR BID + DTG BID – CD4+ kept declining increased to DRV 800/100 BID in March 2016, and switched TDF to TAF in Aug 2017 all of which had little impact as VL rising, CD4+ continued to decline
    - Nov. 2019: HIV VL = 5,555 copies/mL, CD4 = 40 cells/mm^3
    - 2019 genotype: high level resistance across the board with no options – **six class resistance with no active drugs remaining**
- New ARV drug option: fostemsavir – attachment inhibitor
    - Studied in Brighte trial (Kozal et al. Fostemsavir in Heavily Treatment-Experienced Adults with Multidrug-Resistant HIV. NEJM. 2020:382:1232-1243).
    - VIIV willing to provide fostemsavir compassionately but need another active agent.
- ETR stopped Dec 2019 in anticipation of islatravir (ISL)/doravirine (DOR) phase 3 trial enrollment in March 2020 (option to combine with Fostemsavir approved by Merck).
- March 2020 – pandemic – all research stops.
- Screened Aug. 2020 and started on ISL 0.75mg/DOR 100mg daily, fostemsavir 600mg BID+ OBT of DRV 600mg/RTV 100mg BID, DTG 50mg BID on Oct. 1, 2020!
    - HIV VL undetectable Nov. 2020 to Mar. 2021; March 2021 CD4 = 110 cells/mm^3 (6%)
    - April 2021 HIV Pharmacist Education Day Discussion:
        - Would you simplify? What? When?

Updates over the past year:

- HIV VL still undetectable in May 2022; May 2022 CD4 = 182 cells/mm^3
- MD did not simplify treatment; no changes made to ARV regimen.
- Dec. 2021 – Merck announced clinical holds on studies evaluating ISL for the treatment and prevention of HIV-1 infection based on previously announced observations of decreases in total lymphocyte and CD4+ T-cell counts in some participants receiving ISL in clinical studies.
    - Participants in studies of DOR/ISL who were started on treatment will continue to receive study medication
- Patient had COVID-19 vaccines: Pfizer May 20, 2021, Moderna July 8, 2021, Pfizer March 23, 2022. COVID-19 RNA positive Jan 26, 2022; mild symptoms: sore throat, cough, fatigue x 10 days. Patient did not receive Paxlovid which had just come to market in Canada in Jan. 2022.
- Discussion
    - Focus on future options:
        - Lenacapavir (LEN): HIV-1 capsid inhibitor; being studied in CAPELLA trial as SC administration with Q6m dosing
        - Would you simplify with LEN? If so, removing DRV/RTV would be an option.
        - Alternative idea offered was to add LEN, drop DOR, and keep DRV/RTV – not for simplification, but more so regimen durability.
    - If patient hadn't been switched to DOR/ISL, fostemsavir, + OBT would he have survived the Jan. 2022 COVID infection?

Alissa is currently transitioning from her HIV pharmacist role to an oncology pharmacist position.

Case #3: To Cabenuva or Not to Cabenuva?

Deborah Yoong in Toronto, ON

Cabenuva Overview:

- Cabotegravir long-acting injection (CAB LAI) + rilpivirine long-acting injection (RPV LAI) approved by Health Canada in March 2020 as a complete ARV regimen for treatment of HIV-1 infection to replace current ARV regimen for patients who are virologically stable and suppressed.
- Two formulations available:
    - Cabenuva 2mL = CAB 400mg/RPV 600mg
    - Cabenuva 3mL = CAB = 600mg/RPV 900mg
- Administered on once monthly or q 2 month IM schedules (higher dose given in q 2 month schedule);
- Long half-lives: RPV LAI = 13-29 weeks; CAB LAI = 6-12 weeks

Review of Data:

- FLAIR
    - Eligibility criteria:
        - ARV Tx naïve with HIV-1 RNA ≥ 1,000 copies/mL; HBsAg negative; NNRTI RAMs excluded
    - Design:
        - All enrolled participants took DTG/ABC/3TC single-tablet PO regimen for 20 weeks after which they were randomized to either remain on PO DTG/ABC/3TC or take PO CAB + RPV x 4 weeks followed by CAB 600mg/RPV 900mg IM x 1 and then monthly IM CAB 400mg/RPV 600mg.

- VL ≥ 50 copies/mL: 2.1% (6/283) LAI vs 2.5% (7/283) PO

- ATLAS
  - Eligibility criteria:
    - ARV experienced taking PI-, NNRTI-, or INSTI-based regimen with 2 NRTI backbone; excluded active Hep B, previous virologic failure, INSTI or NNRTI RAMS
  - Design:
    - All enrolled participants randomized to continue current PI-, NNRTI-, or INSTI daily PO ARV regimen or to take PO CAB/RPV x 4 weeks followed by CAB 600mg/RPV 900mg IM x 1 and then monthly IM CAB 400mg/RPV 600mg.
  - VL ≥ 50 copies/mL: 1.6% (5/308) LAI vs 1% (3/308) PO
- ATLAS-2M
  - Eligibility criteria:
    - ATLAS patients (either arm; if in the PO standard of care group, these folks took 4 weeks of PO CAB/RPV before starting injectable CAB/RPV.
  - Design:
    - All enrolled participants randomized to CAB 400mg/RPV 600mg IM q 4 weeks or CAB 600mg/RPV 900mg IM q 8 weeks
  - VL >50 copies/mL: 9/522 (2%) receiving q8w vs 5/523 (1%) on q4w

Results:

- For maintenance of virological suppression of HIV-1 CAB+RPV IM Q4W is non-inferior to oral standard of care; CAB+RPV IM Q8W is non-inferior to Q4W
- Injection site reactions (>80%), mild-moderate, ~ 3 day duration, mostly resolving within 7days, incidence decreases with time, Q8W > Q4W dosing
- Other A/Es: nasopharyngitis, headache, URTI, diarrhea
- Enrolled patients had good adherence and engaged in care

- Factors associated with virologic failure:
  - **Proviral RPV RAMs**
  - **HIV-1 subtype A6/A1**
  - **BMI ≥ 30 kg/m^2**

  } **2 required to increase risk**

  - Week 8 RPV trough concentrations

Clinical cases

Case #1:

36 y.o. male. HIV Dx 2019. HCV neg, hepatitis B immune. Busy running several restaurants and missing meds 1-3x/week

Date	Regimen	Viral load (copies/mL)
Apr 2019 – May 2019	Genvoya + darunavir	67,498
May 2019 (after baseline genotyping returns showing: no RT/PI mutations, INSTI genotyping failed, clade B) – Feb 2022	Genvoya	< 40

Patient switched to Cabenuva in Feb 2022 with HIV VL suppression maintained.

Case #2:

54 y.o. female wishing to switch to Cabenuva. HIV Dx 1999. No previous genotyping, clade unknown, Hep C neg, Hep B non-immune, depression, hypertension, BMI=35kg/m^2

Date	Regimen	Viral load (copies/mL)	comment
2008 – 2018	AZT/3TC + NVP TDF/FTC/EFV ABC/3TC + NVP TDF/FTC/RPV ABC/3TC + NVP	VL<50	simplification nausea from RPV
2018 – 2019	ABC/3TC/DTG	VL<50	weight gain
2019 - current	ABC/3TC + NVP	VL not detected	weight has remained stable

Current meds:

- ABC/3TC + NVP
- pantoprazole 40mg daily
- levothyroxine 0.05mg daily
- candesartan 16mg daily
- HCTZ 25mg daily
- aripiprazole 10mg daily
- duloxetine 90mg daily
- quetiapine 25mg daily

Considerations and Plan Devised:

- PPI + PO lead-in with PRV, had nausea with RPV in past.
- Weight gain on DTG maybe same concern with CAB
- BMI of 35 kg/m2 – get around this by using long needles
- Patient still wished to proceed; team opted to go with a step-wise plan where she comes off PPI first and then does PO lead in with RPV/CAB and then q monthly RPV/CAB IM injections to check-in more frequently… patient has been traveling so currently stuck in the PPI cessation phase.

Discussion:

- 3-year ATLAS 2M data could justify support q monthly IM CAB/RPV choice over q 2 month option
- Alternative could have been straight to injection and avoid PO lead-in as there is data for this.
- Question about how much the aripiprazole contributed to weight gain, especially if the NVP was inducing aripiprazole and then when NVP was changed to DTG the induction property was removed and aripiprazole concentration would be increased…

Case #3:

28. yo. male admitted for psychiatric deterioration from schizophrenia. Dx: HIV Ab+, HCV Ab+, HBV immune. Baseline labwork: HIV VL 2,450,000 copies/mL, CD4 65 cells/mm^3, genotyping: K103N mutation, clade B virus. Non-ARV Meds: SMX/TMP 400/80mg PO daily, paliperidone sustenna 150mg IM q4w, benztropine 2mg PO prn

Date	Regimen	Viral load (copies/mL)
November 19, 2021	Start Biktarvy	2,450,000
December 29, 2021	Biktarvy	1860
January 19, 2022	Biktarvy	432
February 18, 2022	to start Cabenuva	726,000
March 23, 2022	Cabenuva	154
May 19, 2022	Cabenuva	73

Decision was made to proceed with original Cabenuva based on the ViiV compassionate program data presented at IAS in July 2020 in which 28/35 (80%) viremic at baseline and 16/28 (57%) achieved virological suppression.

Case #4:

55 y.o. male. HIV Dx 1998. Came under their team's care in 2003. no previous genotyping available, clade unknown. HCV neg, hepatitis B immune. Current meds: sildenafil PRN

Date	Regimen	Viral load
1999 x 6 months	AZT, ddI	viremia
2000 x 2 years	AZT/3TC + NVP	viremia
2002 x 6 months	ABC + 3TC + NFV	viremia
2003 – 2005	3TC + d4T + TDF + ATV + RTV	<50
2005 – 2011	TDF/FTC + ATV + LPVr	<50
2011 – 2016	TDF/FTC + RAL + DRVr 600/100 BID	ND
2016-2017	TDF/FTC + DTG + DRV/c	ND
2017 – current	DTG + DRV/c	ND

Consideration:

- Viremia on AZT/3TC + NVP – does he have NNRTI resistance history? Decision made to NOT go with Cabenuva given outstanding questions around viremia on NVP containing regimen and potential cross-resistance to RPV.

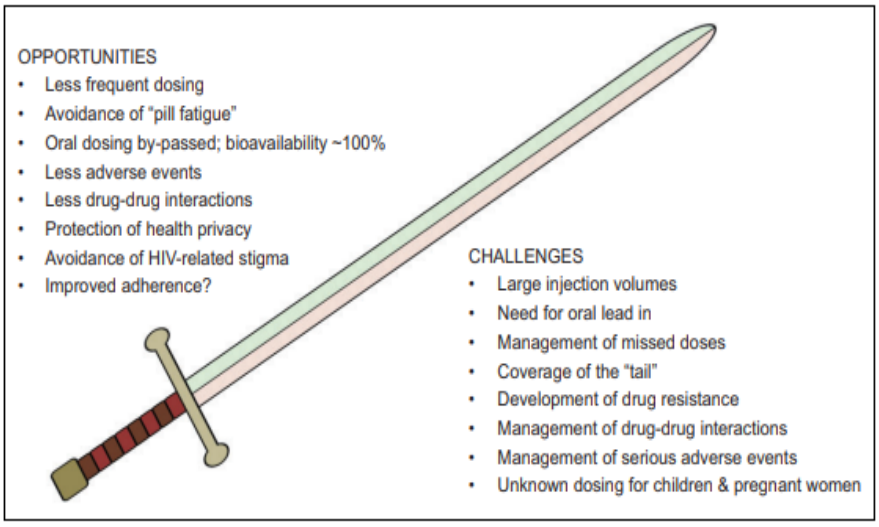
Case #5:

50 y.o. male. HIV Dx 2000 (India). HCV neg, hep B immune. Genotyping not available, clade unknown. Current non-ARV meds: vitamin D, omega-3 fatty acids, multivitamin, zinc

Date	Regimen	Viral load
Oct 2020		76
Jan 2021	TDF/3TC/DTG	~10,000
Apr 2021		ND

What to do? That is the question given no genotyping and clade unknown…Question posed as to whether it would make sense to switch to Odefsey x 6 months and if okay then go with Cabenuva – that would rule out NNRTI resistance. Most low-to-middle income countries have switched to a DTG based ARV regimen given more than 10% NNRTI baseline resistance.

Long-acting ARV therapy: opportunities and challenges (Scarsi K et al. JIAPAC 2021)



- inactive against hepatitis B virus
- cold chain requirement
- arrangement for injections

Role of pharmacist

- Educate and inform
- Screen for eligibility
- HIV-1 adults with sustained virologic suppression (~6 months)
- No known or suspected resistance to CAB or RPV, clade A6/A1
- No active or occult HBV infection
- Not pregnant or planning on becoming pregnant
- Not receiving medications with drug interactions with CAB or RPV
- Review risks/benefits
- Convenience? Missed dose management

COVID Forum: Pharmacists' Journey through Rollout of Vaccines, Testing, and Therapeutics

Moderator: Linda Robinson
Panel: Sue Gill, Mina Tadros, Ben Gunter

Optimizing Covid-19 Processes by Mina Tadros, Maple Leaf Medical Pharmacy, Toronto
COVID-19 services: vaccinations asymptomatic rapid antigen tests, take home rapid test kits, Paxlovid treatment

Vaccine Challenges:

- Equal access among all patients (general public and current patients)
    - Pharmacy patients expecting prioritization over the public
    - Lack of honesty about eligibility criteria
- Scheduling constraints/vaccination waste
    - Originally vaccine scheduling was done via manual calendar → not sustainable!
    - No-shows; more noticeable when booking patients 3 weeks out as they would find a vaccine spot elsewhere and then forget to cancel their original appointment. This improved once they starting only booking out to a max. of 5 days.
- Workflow and workload
    - Processing – 3x work for 1 RX!
        - Patient consent sheet
        - COVaxON Input
        - Kroll (Profile creation + billing)

Improvements made to address challenges

- Online self-schedule calendar
- Email consent during registration
- Barcode scanner to read healthcard for profile creation
- Automated phone system with directions
- All in one point of sale – high volume
- Sign up for one-mail – Up to date information

Covid Services and Community Pharmacy by Ben Gunter, Shoppers Drug Mart (SDM) in Ottawa
Similar experiences and challenges as highlighted by Mina earlier were experienced at SDM. Staffing shortages encountered which impacted balancing dispensing and clinical work.

Expanded scope of practice successes and challenges

- COVID Vaccine
    - Scheduling, phone calls and procurement
        - SDM was using a manual calendar for scheduling until summer of 2021.
    - Keeping up with ever changing eligibility criteria
        - This meant keeping all staff working in pharmacy, and front store, up to date with current eligibility.
    - Questions and answers from patients and prescribers
    - Maintaining accurate COVAXON files
        - Out of province/out of country vaccine status
        - Important for when vaccine passports came into effect and people needed at least 2 doses of vaccine in order to enter many establishments
    - Peak patient demand times

        - 3rd (Dec/Jan) and 4th (Apr/May) dose waves
    - Managing supply and demand
    - Limiting vaccine wastage

COVID Testing
- Public and Private PCR Testing
    - Providing provincial support in the COVID PCR testing programs
        - Removal of the majority of publicly funded PCR testing in January 2022
        - Select patients still qualify; eligibility updates and changes
    - PCR private testing for international travellers (select countries)
- Private Rapid Antigen Testing (travel and small businesses)
- Public Rapid Antigen Take Home Test Kits
    - Shift to patient at home testing with Rapid Antigen Tests
        - Testing techniques – nasal vs. buccal/nasal
        - Proper sample collection and interpretation of results
- Keeping patients informed of current Public Health guidelines

Paxlovid Dispensing
- Assessing Paxlovid criteria eligibility
    - "Grey area" / criteria "e" (the individual is assessed as being at higher risk of severe COVID-19 based on their age, vaccination status, and risk conditions (excluding risks due to travel) by their prescriber)
- Obtaining a complete patient profile for new/not on file patients
    - 25% of individuals getting Paxlovid at their pharmacy were not their patients but were seeking Paxlovid there because other pharmacies didn't have it readily available.
- Communication with prescribers
    - Rx clarifications
    - Renal function data
- Drug interaction management
    - Needed to get medication lists from patients' regular pharmacies to perform drug interaction checks

What's Next for Expanded Scope of Pharmacist Practice?
- Minor Ailments prescribing coming January 2023.
- Proof of success with Point of Care testing
    - Will this lead to HIV Rapid Test coverage by ODB?
- Will PreP and PEP prescribing be on the horizon?

Covid-19 Therapeutics in Community Settings by Sue Gill Michael Garron Hospital (MGH), Toronto East Health Network

MGH's Paxlovid Experience
- Started dispensing Paxlovid in early March 2022. Low weekly dispensing initially as few patients met eligibility criteria. Weekly dispensing peaked in mid-April with 41 dispenses the week of April 23. Early on patients were simpler and on few medications, so they were easier to work-up but when eligibility expanded it meant older and more complex patients were eligible and this translated to more lengthy medication lists.

- Paxlovid dispensing mirrored the vaccination rollout protocols used by the Toronto East Health Network for their high-risk population
    - High level process for someone who presents at the Covid Assessment Centre (CAC) (just outside emergency department) and tests COVID-19 positive and is eligible for Paxlovid therapy:
        1. Patient info flagged to doctors via Hypercare.
        2. Paxlovid RPh completes MedRec for treatment
        3. CAC Nurse completes bloodwork
        4. MD gives final approval for treatment
        5. RPh dispenses appropriate treatment
- All patients had a MedRec note called "Paxlovid Review and Recommendations" placed on their EMR about Paxlovid initiation and any relevant drug interactions identified and the management plan. They opted to hold interaction inhibited medications (e.g., rosuvastatin) x 7 days when Paxlovid was prescribed. This note was particularly important for patient follow-up encounters.
- Paxlovid patients were enrolled in a virtual ward.
    - Day 1-5: patient is followed by virtual ward nurses.
    - If any medication changes were made with initiation of Paxlovid treatment, RPh calls patient on Day 7 to discuss resuming usual medications (and doses) and assesses Paxlovid tolerability.
    - Day 28: physician assistant calls to assess efficacy, tolerance, and mis-adherence issues due to medication alterations.
- Just over 330 Paxlovid recipients have gone through the MGH clinic and In Sue's experience, most people tolerated Paxlovid well; most common side effects were taste disturbance and headache.
- Review of the MGH drug-drug-interaction database for Paxlovid recipients will be happening with goal of publishing their findings as the population they are using Paxlovid in was different than what was studied (young, unvaccinated, otherwise fairly healthy population)
    - Example of a case they treated: 73 y.o. male living with HIV infection on Genvoya who presented for testing after 3 days of symptoms: fever, cough, rhinitis, and sore throat. Had received 4 doses of COVID vaccine. Comorbidities: MI (2004, stent x 1), HTN, dyslipidemia, GERD. Weight 88kg, SCr = 96 umol/L (est. CrCl: 76 mL/min) –-> use Connecting Ontario to access labwork.

Commentary on Paxlovid

- Paxlovid has standard dosing of 300 mg nirmatrelvir/100mg ritonavir BID x 5 days for CrCl > 60 mL/min. Nirmatrelvir comes as 150mg tablets; 2 tablets are taken to get the 300 mg dose.
- Paxlovid packaging was very good with respect to labelling by the manufacturer.
    - With respect to renal dosing of nirmatrelvir for eGFR 30 to 59 mL/min, the package was actually designed such that one 150mg tablet of nirmatrelvir is to be popped out from both the morning and evening sections of the package and a renal dosing label was to be placed over the popped-out dose sections of the package.
    - New data has recently come out about dosing for CrCl < 30mL/min.
- Sue referenced the Science Table Paxlovid drug interaction report but didn't elaborate on it as a presentation later in the day by Alice Tseng would be covering this in depth. Another helpful drug interaction resource is the Liverpool COVID19 interaction checker www.covid19-druginteractions.org/checker

Evusheld (tixagevimab & cilgavimab) – 2 cases received this niche product in early June

- During discussion, comment from Kingston that they are leaning away from offering Evusheld

COVID Reinfection vs. Rebound and Paxlovid Retreatment Discussion

- How do you know when it is reinfection vs rebound COVID when patients are treated with Paxlovid? That is indeed a good question, without a clear answer!
- Pierre has been involved in the treatment of about 500 cases in Ottawa and has treated 3-5 rebound COVID-19 cases. In these situations, the re-treatment supply was being provided by the hospital as there was uncertainty about be able to do this in the community pharmacy setting. The rationale for retreatment of these rebound cases was looking at the risk of the patient being admitted to hospital.
- Tessa reported that in Kingston, treatment for rebound COVID post-Paxlovid treatment was mostly being done in their very immunosuppressed patients as a conservative approach.

Overall, a theme arose during the COVID forum discussion of how pharmacists made significant impact with limited recognition and limited reimbursement for their impact during the pandemic.

Lunch Plenary: Update on PrEP Options in Ontario *by Dr. Darrell Tan in Toronto, ON*

Deborah Yoong introduced Dr. Darrell Ta, who has been consumed by a focus on monkeypox lately; monkeypox is embedded in local sexual networks and has been for awhile but it is just recently being realized; should be on everyone's radar because it must not be ignored. Atypical presentation: skin lesions +/- flulike symptoms +/- lymphadenopathy OR unusual presentation of ? STI

Why do we need long-acting PrEP options?

- Biopsychosocial explanation:
  - Bio: Dysphagia, side effects, malabsorption, cognitive difficulty
  - Psycho: Pill fatigue, anxiety/depression, preference for other modes of administration
  - Social: Privacy, convenience
- The key determinant of PrEP efficacy is medication adherence
- More choice is associated with more uptake – example of contraception options
  - Survey done in MSM in Toronto by Tan et al. – more PrEP choices = more (predicted) uptake
- PrEP uptake is going up slowly; policy changes such as Health Canada indication and ODB coverage in Ontario influenced this

What are long-acting PrEP options?

Present: oral TDF/FTC or TAF/FTC tablets

Emerging: intravaginal ring or injectable

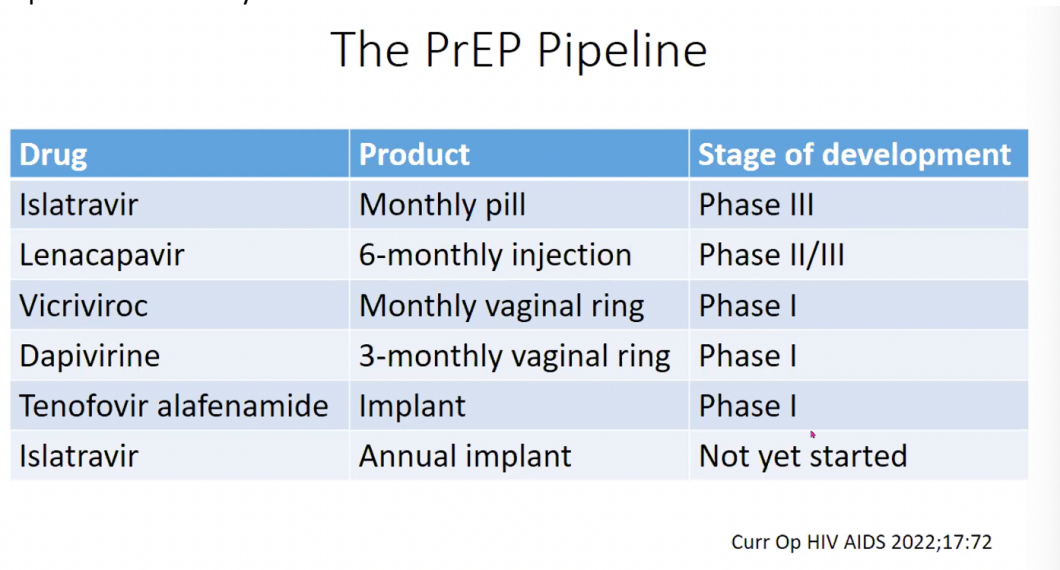
- Dapivirine vaginal ring
  - Relative risk reduction: 31% (95% CI=1%,51%); 27% (95% CI = 1%, 46%). (NEJM 2016; 375:2121; NEJM 2016;375:2133.)
  - Not coming to Canada because oral PrEP results were better
  - Argument is that PrEP options that are less effective than oral PrEP at preventing HIV can still have big impact if they attract 'new' users.
    - WHO recommends the dapirvirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection.
- HPTN 083 and 084: LA IM CAB Q2M vs. Daily Oral FTC/TDF for PrEP
  - International, randomized, double-blind phase IIb/III (083) and phase III (084) trials;

- LA IM CAB met criteria for superiority vs. daily oral FTC/TDF in both trials
  - HPTN 083 (NEJM 2021;385:595):
    - 4566 MSM and transgender women at high risk of contracting HIV (condomless receptive, 5+ partners, syphilis, rectal GC/CT, stimulant drug use)
    - LA IM CAB was 66% more effective than daily oral FTC/TDF PrEP
    - Injection site reactions: only 2.2% of LA IM CAB participants permanently discontinued
    - More weight gain in CAB group than TDF group, although difference remains stable after a year
    - LA IM CAB PrEP failures: n=7 for infected despite on-time injections (CROI 2022)
    - December 2021: FDA approved CAB for PrEP; FDA said could go direct to injection and skip an oral CAB lead-in
  - HPTN 084: 3224 cisgender women in sub-Saharan Africa; LA IM CAB was 88% more effective than daily oral FTC/TDF PrEP
    - Pregnant and breastfeeding women are often excluded from trials; the investigators of HPTN 084 are opening up investigations to address this group

Cabotegravir – the fine print:

Clinical	Logistical
• Tail phase • Rare breakthrough infections • HIV RNA testing for monitoring • Oral lead-in • Timing of doses/oral bridging • Weight differences	• Health Canada approval • Public funding • Patient assistance programs • Locations for administration • Personnel for administration • Record-keeping for injections

Future: implant and antibody



Islatravir will probably be a no-go now due to concerns about leukopenia.

How do we procced?

- Raising awareness
- Community consultation
- Collaborative planning

Discussion question: primary care providers in rural areas are already hesitant to prescribe PrEP. Will more PrEP options make primary care providers more hesitant to prescribe PrEP? Excellent question – it certainly could.

Announcements re: Upcoming Educational Events

1. International Workshop on Clinical Pharmacology of HIV, Hepatitis, and Other Antiviral Drugs - Hybrid event in Barcelona and online in September 2022.
2. Dr. Darrell Tan is doing a virtual webinar on Monday, June 13 on Monkeypox www.ohtn.on.ca/hive

Cases to Share/Solve

Case A: Return of the MAC: A Case of Disseminated MAC in a Complex Patient with AIDS

Sharan Lail in Toronto, ON

Patient ID:

40 y.o. HIV+ man with uncontrolled HIV VL and low CD4 count despite being on ART, complicated by opportunistic infections (disseminated MAC, CMV retinitis). Smokes 1 joint/day, 1 pack of cigarette/day. Rare alcohol use.

Timeline

- Jan 2019 – HIV diagnosis with OI (admitted with PJP, aspergillosis, thrush esophagitis and MAC colonization). CMV positive, not treated. HIV VL = 91,868 copies/mL, Genotype = wild type. CD4 14. Started RAL/TAF/FTC
- Apr 2019 – HIV VL = 91 copies/mL, CD4 70 (17%). ART: RAL/TAF/FTC
- May 2019 – ART switch from RAL/TAF/FTC to Genvoya (EVG/c/FTC/TAF) to simplify regimen
- July 2019 – ART stopped due to cost
- July 2020 – admitted for pneumonia. HIV VL 967,202 copies/mL, CD4 202 (19%). Started Biktarvy (BIC/TAF/FTC), MAX card given. Started Septra DS for PCP prophylaxis.
- Aug 2020: MAC in blood, sputum and stool samples – started clarithromycin + ethambutol
- Dec 2020 (?) – ART stopped
- June 2021 – admitted for disseminated MAC (sputum, splenic biopsy). Restarted on clarithromycin + ethambutol + rifabutin. Clarithromycin was changed to azithromycin and then stopped due to QT-prolongation. Started IV ganciclovir induction + valganciclovir maintenance for CMV, received surgery for retinal detachment. HIV VL > 1 million, transferred to Casey House. ART started: DTG + ABC + 3TC + DRV/r
- Aug – Oct 2021: uncontrolled HIV VL while on ABC/3TC/DTG + DRV/r at Casey House
    - Aug 2021: VL = 1.7 million copies/mL. CD4 = 2 (2%)
    - Sep 2021: VL = 858,000 copies/mL CD4 = 2 (2%)
    - Oct 2021: VL = 1.3 million copies/mL, GT = WT – non R5 tropic. CD4 = 5 (3%). Discharged from Casey House

- Dec 2021 – VL = 711,000 copies/mL, genotype = wildtype CD4 = 12 (6%). ART: ABC/3TC/DTG + DRV/r. Dec 2021 cardiologist consult: Pt does not have long QT syndrome. QT-prolongation should not alter treatment
- January 2022 Sharan received pharmacist consult requesting evaluation of ART regimen due to continued viremia

Medications patient was supposed to be taking at time of pharmacist consult:

HIV: ABC/3TC/DTG+DRV/rtv
Disseminated MAC: Ethambutol + rifabutin
CMV (2nd prophylaxis): valganciclovir 450mg q2days
PCP/toxo prophylaxis: Atovaquone 1500mg daily CC
Oropharyngeal candidiasis: fluconazole 200mg x 14 days
Pancytopenia: GCSF 300 mcg SUBCUT 2/7
QT prolongation: bisoprolol 2.5mg daily, magnesium oxide daily
Hypothyroidism: levothyroxine 12.5mg daily
Anxiety/depression: olanzapine 5mg daily

Adherence: What was he really taking at time of pharmacist consult?

- Compassionate supply provided by Casey House for 1 month upon discharge
- Patient would not engage in discussion with Casey House SW to get ODSP or Trillium; was intent on going back to work

Why does the patient have viremia?

Resistance to ART? Unlikely resistant to ABC/3TC/DTG + DRV/RTV
Non-compliance? Fill dates indicate non-compliance; missed appointments
Malabsorption secondary to MAC? CMV?

- Review of the August 2021 blood sample from the Casey House admission shown low/absent darunavir and ritonavir levels although dolutegravir was present.
- Case report found about protein-losing enteropathy caused by disseminated MAC in a patient receiving ART had some similarities to the patient.
- Acetaminophen absorption test considered another way to check for drug absorption, but patient didn't engage with this idea.

Outcome

- Patient would not engage in care (return calls, attend appointments)
    - He returned 1 email from Sharan
- GP did home visit, convinced him to go to ER
    - Patient sent home from one ER with amoxicillin script
    - 2 days later went to another ER -> admitted
        - Day 1: GIM for hepatitis, AKI, and pericardial effusion
        - Day 2: code stroke (facial asymmetry)
        - Day 3: unresponsive -> PEA -> shocked -> intubated -> ICU.
        - Advanced illness, overall physiological frailty, complications of HIV/AIDS, multi-organ failure, and lack of neurological recovery, his prognosis for survival and recovery was deemed very poor. Discuss goals of care with parents -> requested palliation. Patient passed away without distress shortly after extubation.
- Later, the parents found ++ medication bottles in the patient's home suggesting at least intermittent non-adherence was a factor.

Challenges Encountered During this Case:

Obtaining history required review of/discussion with

- Connecting Ontario → Discharge summaries
- Community pharmacist
- Casey House pharmacist

Mental health

- Patient focused on returning to work
- Understanding of disease
- Undiagnosed personality disorder
- Engagement in care – missed appointments, pharmacy deliveries, calls

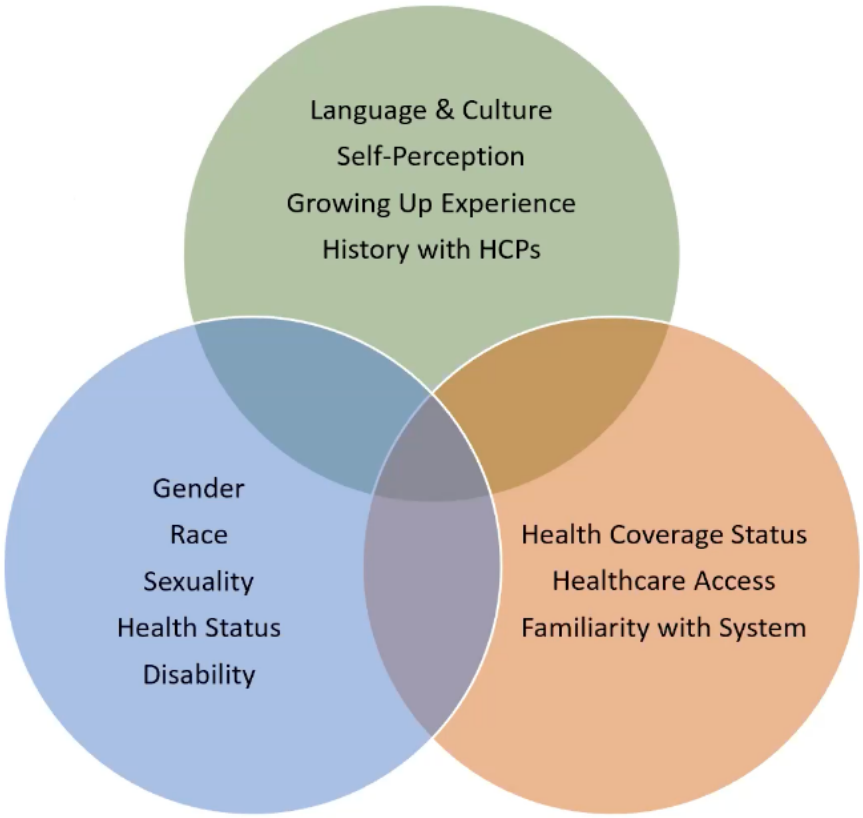
Discussion comment – if patient had been willing to engage in care, perhaps Cabenuva could have been considered as a way to get around drug absorption concerns related to OI infections

Case B: PrEP Access Barriers for Newcomers

Andrew Schonbe in Toronto, ON

1/5 of the patients he sees are newcomers to Canada.

Considerations in this population:



Case 1: Recently moved to Canada for work; received first Rx for PrEP but significant concerns about privacy – concerns employer and family finding out if they started PrEP (has work insurance), self-perception of being on PrEP, judgement in access.

- Solutions to address PrEP Awareness and Stigma:
    - Utilize outreach channels
    - Provide a welcoming space – your commitment
    - Explain confidentiality and the process early on
    - Provide care to all genders and orientations
    - Get across PrEP is common (e.g., diverse signage, language use)
    - Be mindful some info may be withheld
    - Anonymity supports: packaging, processing, shipping, testing options

Case 2: International student interested to work and live in Canada post-graduation. Familiar with PrEP but not sure if can start without provincial coverage. Concerns: cost of care and medication, how to access care, school finding out, impacts on immigration.

- Solutions: clinic and testing access
    - Local public health or community organizations
        - Even if for partial labwork
    - Local PrEP service providers
    - Online PrEP service providers
    - May have private coverage for lab/clinic services
- Solutions: PrEP affordability
    - Local and provincial programs (e.g., PrEPStart)
    - IFH coverage
    - Patient Assistance Program (e.g., Gilead)
    - Workplace, school insurance
        - Concerns re: school, work finding out
    - Low-cost local service providers

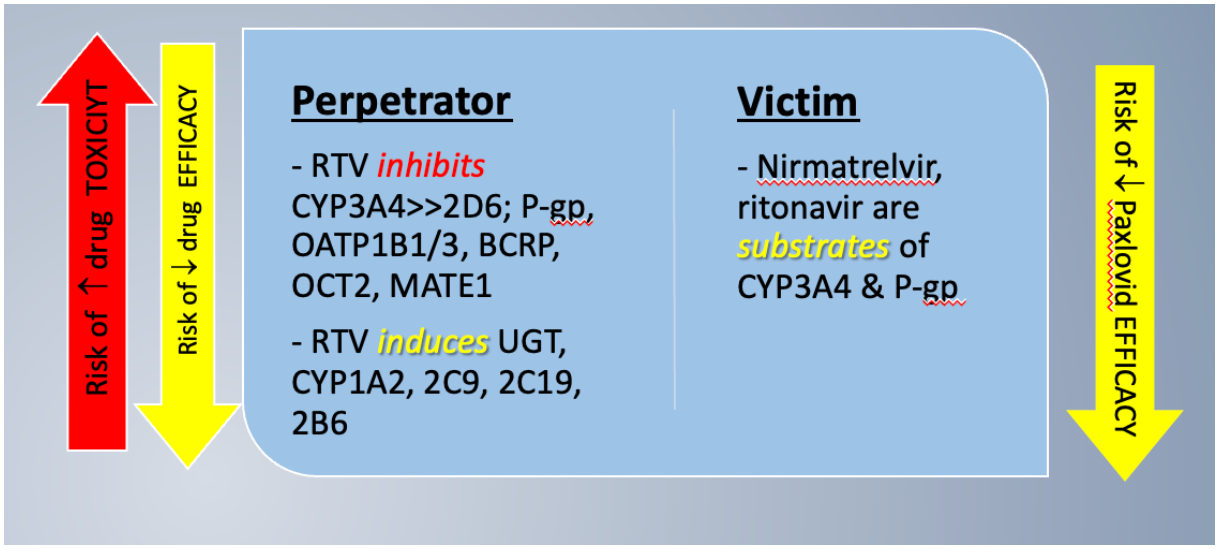
  Patients may need guidance and prompting

Case 3: Refugee status claim is being processed due to persecution, violence. Knows some words in English but conversations are difficult. Is not familiar with PrEP. Negative history with healthcare providers. Concerns: fear in accessing care, safety concerns, internal and external stigma, cost, daily medication use.

- Solutions: cultural and language barriers
    - Team diversity and cultural awareness training
    - Clear guide on how to start PrEP
    - Resources and info of sexual health
    - Referral to ASOs and support programs – socialization/inclusion
    - Truly private/safe zones when communicating
    - Accessible channels for support and routine follow-up by healthcare provider

- Hire multilingual providers
- Communicate via translators
- Communicate via messaging (e.g., text, email)
- Patients may bring friend to assist
- Schedule longer appointments (or break into parts)
- Multilingual education materials

Case C: Paxlovid (nirmatrelvir/ritonavir) drug Interactions: practical management strategies
Alice Tseng in Toronto, ON



Drug interactions in product monograph:

- 37 contraindicated drugs (19 drug classes)
- 118 established/potential drug interactions (32 drug classes)

What's different between managing DDIs with Paxlovid vs other boosted (HIV) PIs?

Paxlovid:

- START within 5 days of symptom onset
- TREAT for 5 days
- Renal dose adjustment

HIV boosted PI:

- No strict window for starting therapy
- TREATMENT: chronic
- No renal dose adjustment

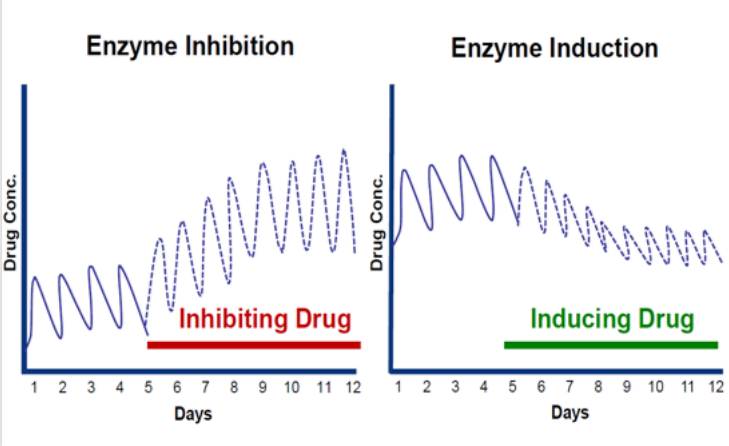
When NMV/ritonavir CANNOT be Used and Must use Alternative COVID Agent

VICTIM: Nirmatrelvir/r + potent CYP3A4 inducers *within last 14 days*

- Stopping inducer (e.g., rifamycins, anticonvulsants, St. John's wort, apalutamide, enzalutamide) will not mitigate this interaction as need to start NMV/r within 5 days

PERPETRATOR: use of drugs with long t1/2 or narrow therapeutic index/critical indication

- Stopping drug (such as antiarrhythmics, fentanyl, some antipsychotics, PAH drugs) will not mitigate interaction or may cause more harm



- Risk of drug toxicity
- Risk of decreased drug efficacy

	Inhibitors	Inducers
Onset (max effect)	1-2 days	1-2 weeks
Offset	2-3 days	2-4 weeks

Many drug-drug interactions in monograph are not clinically relevant over period of NMV/r treatment (e.g., CYP 2D6 substrates and many antidepressants; this was taken from data in which ritonavir dose was at an HIV treatment dose and CYP 2D6 impact was more likely).

Challenges/considerations when managing nirmatrelvir/ritonavir drug interactions:

- HOLD drug: specialist prescriber approval?
- CHANGE dose: splitting pill or new Rx? Correctly restarting usual dose
- REPLACE drug: new Rx, drug coverage, dispensed on time, make sure no overlap with previous drug
- MONITOR: TDM, lab turnaround? Isolation requirements

Bottom line: pragmatic, practical approach needed because must start nirmatrelvir/ritonavir within 5 days and treat for 5 days…. Clear communication is important.

Survival Tips:
Try to do as much pre-emptive work as possible!

- identify higher-risk patients
- creatinine/eGFR within last 3-6 months
- get complete, up to date med list
- identify high-risk DDI meds, try to loop in other specialists to formulate plan
- counsel patient: reach out as soon as symptoms begin

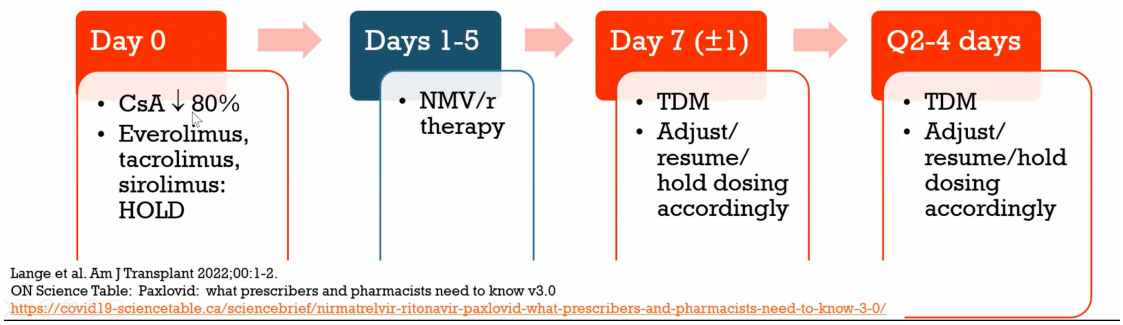
Suggestions for Rx:

- Have on HOLD at pharmacy
- Ask MD to include cell number in case pharmacist needs to reach them outside office hours
- Add creatinine clearance if <60 mL/min

Paxlovid Drug Interaction Resources:

- https://www.covid19-druginteractions.org/
- https://covid19-sciencetable.ca/sciencebrief/nirmatrelvir-ritonavir-paxlovid-what-prescribers-and-pharmacists-need-to-know-3-0/
- https://covid19-sciencetable.ca/sciencebrief/paxlovid-for-a-patient-on-a-doac-2-0/
- https://www.antimicrobialstewardship.com/paxlovid-ddi-oncology

Transplant immunosuppressives extremely sensitive to ritonavir inhibition (eg. tacrolimus 0.5mg once q 7-10 days). Preferred approach is to use alternative COVID agent. However, may be supply/access issues.



Discussion Comments:

Pierre has treated 40-50 kidney transplant patients with Paxlovid and there are some odd cases that don't follow the rules or some patients that don't follow the instructions provided. Having TDM of the immunosuppressants is important. Has recently seen a tacrolimus level of 67 and another one of over 100 (target level is between 4 to 6), which almost makes it appear like these patients didn't stop the tacrolimus at all while taking nirmatrelvir/ritonavir.

Dosing in Renal Dysfunction (eGFR<30 mL/min):

- Not recommended by manufacturer
- Ontario Renal Network guidance document (April 2022)
- Early positive experience (n=19)
  - https://www.ontariohealth.ca/sites/ontariohealth/files/2022-04/PaxlovidClinicalGuide.pdf
  - Brown et al. https://www.medrxiv.org/content/10.1101/2022.05.18.22275234v1 May 21, 2022

CDC Health Advisory re: COVID-19 Rebound after Paxlovid Treatment released May 24, 2022

- Recurrence of symptoms or new (+) viral test after previous (-) test
  - Reported 2-8 days after completing 5 day NMV/r therapy
  - Improved/resolved without additional treatment, median 3 days
- Not considered to be due to reinfection or resistance
- Case series (n=10): viral load during relapse similar to initial infection, transmission reported in 2 cases.
  - Take home message: during the rebound, can be contagious so need to restart isolation for ≥5 days
- Paul Sax questioned if longer Paxlovid treatment duration is needed. FDA says no evidence of benefit at this time for a longer course of treatment (e.g., 10 days rather than 5 days).
  - Comment during the discussion that absence of data doesn't equate to ineffective and that drug interaction considerations may need to be revisited if longer durations of Paxlovid are used.

Case D: Hep C: Fentanyl and Glecapravir/Pibrentasvir

Pierre Giguere in Ottawa, ON

Clinical Scenario : Rx for Maviret 3 tablets PO daily x 8 weeks.

- 42 y.o. male
- Clinical Viewer
  - Creatinine = 86 umol/L
  - AST/ALT = 28/22
  - Platelet = 139
  - HCV ab +ve
  - HCV PCR = 1.8 E6
  - No HCV genotype
- Comorbidities:
  - ADHD
  - Anxiety
- Lifestyle
  - Construction worker
  - Current drug use (recreational)
    - Speed/Xtasy
    - cocaine
- Rx : Citalopram 20mg daily, Vyvanse 40mg daily
- Adherence: 80%

Context

- More than 5,000 people in Canada who had opioid-related death in Jan-Sept 2021.
- Opioid related deaths in Ontario are predominantly impacted by fentanyl.

- Sofosbuvir and velpatasvir have no inhibiting or inducing effects on P450, while Glevaprevir/pibrentasvir is considered a weak CYP3A4 inhibitor

- Key points about fentanyl :
    - Primarily metabolized to inactive metabolites through liver and intestinal CYP3A4/5
        - < 10% excreted unchanged renally.
        - Intestinal CYP metabolism accounts for ½ of the liver metabolism
    - No dose adjustment in renal or liver dysfunction
    - Fentanyl patch product monograph warning : Concomitant CYP 3A4 inhibitor use may result in increased fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression.
        - In this situation, close monitoring and observation are appropriate. Therefore, the concomitant use of Sandoz Fentanyl Patch and CYP 3A4 inhibitors is not recommended unless the patient is closely monitored for an extended period of time for signs of respiratory depression, with dosage adjustments made as warranted
    - Fentanyl has a high extraction ratio of 0.85 ('first pass' metabolism)
        - hepatic drug clearance that is sensitive to changes in liver blood flow
        - less sensitive to alterations in binding to plasma proteins or "intrinsic clearance" (changes in hepatic metabolism or biliary excretion).
- Closest indirect comparisons:
    - with glecaprevir/pibrentasvir is with midazolam (CYP 3A4 substrate)
        - Data from an interaction study with midazolam, showed an increase in midazolam AUC of 27%, which was not deemed clinically significant.
    - with fentanyl patch is aprepitant
        - Glecaprevir increased midazolam AUC by 26%, aprepitant increased midazolam AUC by 25%. Aprepitant had no impact on AUC of fentanyl patch.
- Aghemo A, *et al.* Infect Dis Ther 2021; doi: 10.1007/s40121-021-00455-1
    - Real-world data in Europe show glecaprevir/pibrentasvir is well tolerated with high SVR rates regardless of concomitant prescribed or recreational drug use
    - Low rate of serious adverse events. 8 deaths reported - all unrelated to opioid toxicity (e.g., cancer, committed suicide)
- The GRAND Plan Study by Dr. Brian Conway in Vancouver (n=114) demonstrates the preserved efficacy of 8-weeks glecaprevir/pibrentasvir within an inner-city population that are unstably housed and/or actively using fentanyl
    - 50% of the participants were active fentanyl users
    - Of the 2 people who died, neither were taking glecaprevir/pibrentasvir at time of death – they were both waiting to reach SVR.
- Fentanyl > 50x morphine (lethal dose of fentanyl is 1-2 mg compared to 10-12mg with heroin).
    - Considerations: level of contamination with fentanyl, amount of fentanyl used; how it is being taken (smoked, injected), potential small ↑ exposure from DDI, no effect on Cmax. At the end of the day, should recommend naloxone kit and supervised use (never use alone)
- Fentanyl and glecaprevir/pibrentasvir Liverpool Drug Interaction Checker interaction severity recently downgraded to potential weak interaction (yellow)
    - Key message for recreational fentanyl users: given the high degree of variability in fentanyl ingested as a recreational drug it is likely that the greatest driver of adverse effects is the amount ingested rather than the drug interaction.

Take home points

- SOF/VEL pharmacokinetic profile on drugs metabolized by CYP3A4 is good. There are no suspected drug-drug interactions with CYP mediated drugs.
- GLE/PIB is a weak inhibitor with limited impact on CYP3A4 activity
- Fentanyl metabolism is mainly mediated by liver blood flow; contribution of intrinsic liver drug metabolism is minimal. Recretational use of fentanyl should be performed under supervision and with naloxone nearly available, regardless
- Selection of DAAs option should include other characteristics, including pill burden, treatment duration, food requirement and cirrhosis status

Answers to the posed question 'In your opinion, what is the optimal choice?'

1. Glecaprevir/pibrentasvir is a valid treatment option **(true)**
2. The lack of drug-drug interactions with velpatasvir/sofosbuvir makes it preferable in this setting of active drug use **(true)**
3. HCV treatment should be defered until patient is free of drug use
4. I need more information to optimize HCV treatment **(true)**

Closing

Sue Gill thanked Linda Robinson for moderating the day and Tanya Oskam and Diana Campbell and OHTN for their support, as well as all the sponsors. About 56 participants throughout the day and over 70 for Dr. Tan's session suggesting the virtual format helped with access for folks who wouldn't have necessarily been able to make it to Toronto for an in-person session. Perhaps having a hybrid model for next year's event can be considered. Feedback requested on what you would like to learn more about for next year's event is invited. Cases highlighting the past, present, and future provided a good variety of learning opportunities. A shout out was given to the speakers who were novice practitioners years ago and are now experts. This event certainly highlighted the expanded role of pharmacists, as well as the non-pharmacologic supports pharmacists also provide.