Opioid Agonist Therapy 101:
An Introduction to Clinical Practice **Workshop**

HIV and Hepatitis C

Special Considerations for the Management of Opioid Use Disorder

Laurie Ireland MD CCFP

Faculty/Presenter Disclosure

- **Faculty:** Laurie Ireland MD CCFP
- **Relationships with commercial interests:**
  - **None**

Objectives

At the end of this learning activity, the participant will be able to:

- Discuss special considerations in the management of the individual with opioid use disorder and HIV and/or Hepatitis C

Outline

HIV, Hepatitis C, Co-infection

- Epidemiology
- Natural History
- Testing Recommendations
- Treatment
- Opiate Replacement Therapy
- Drug-Drug Interactions
- Prevention

Helena

- 28 yo woman came in for STBBI testing
- She is worried because her boyfriend was recently diagnosed with HIV, not using condoms
- Discloses escalating use of oxycodone/acetaminophen over the last year, snorting up to 20 per day
- Boyfriend has started to inject morphine
- She wants to stop
- Asking to start Opiate Agonist Therapy (OAT)
- Stabilized over 1 week on daily dispensed Buprenorphine/naloxone 12/3 mg
- HIV test result is positive

Human Immunodeficiency Virus (HIV)

- HIV is a retrovirus, 2 RNA
- Spread through blood, genital or rectal fluids, and breast milk
- Primarily transmitted through unprotected sex or sharing needles or drug use equipment with someone with HIV

- HIV infects T-helper or CD4 cells
- CD4 cells direct & coordinate immune system to fight infection
- As CD4 cells decrease, the body loses its ability to fight infections
- Without treatment at risk opportunistic infections and death

HIV Epidemiology

- 36.9 million people living with HIV globally
- Approximately 75,000 people living with HIV in Canada
- 2402 new HIV Infections in 2017
- Transmission Risks in Canada:
  - MSM (46%)
  - Heterosexual (29%)
  - PWID (16%)

PHAC, HIV in Canada—Surveillance Report, 2017

World Health Organization

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS

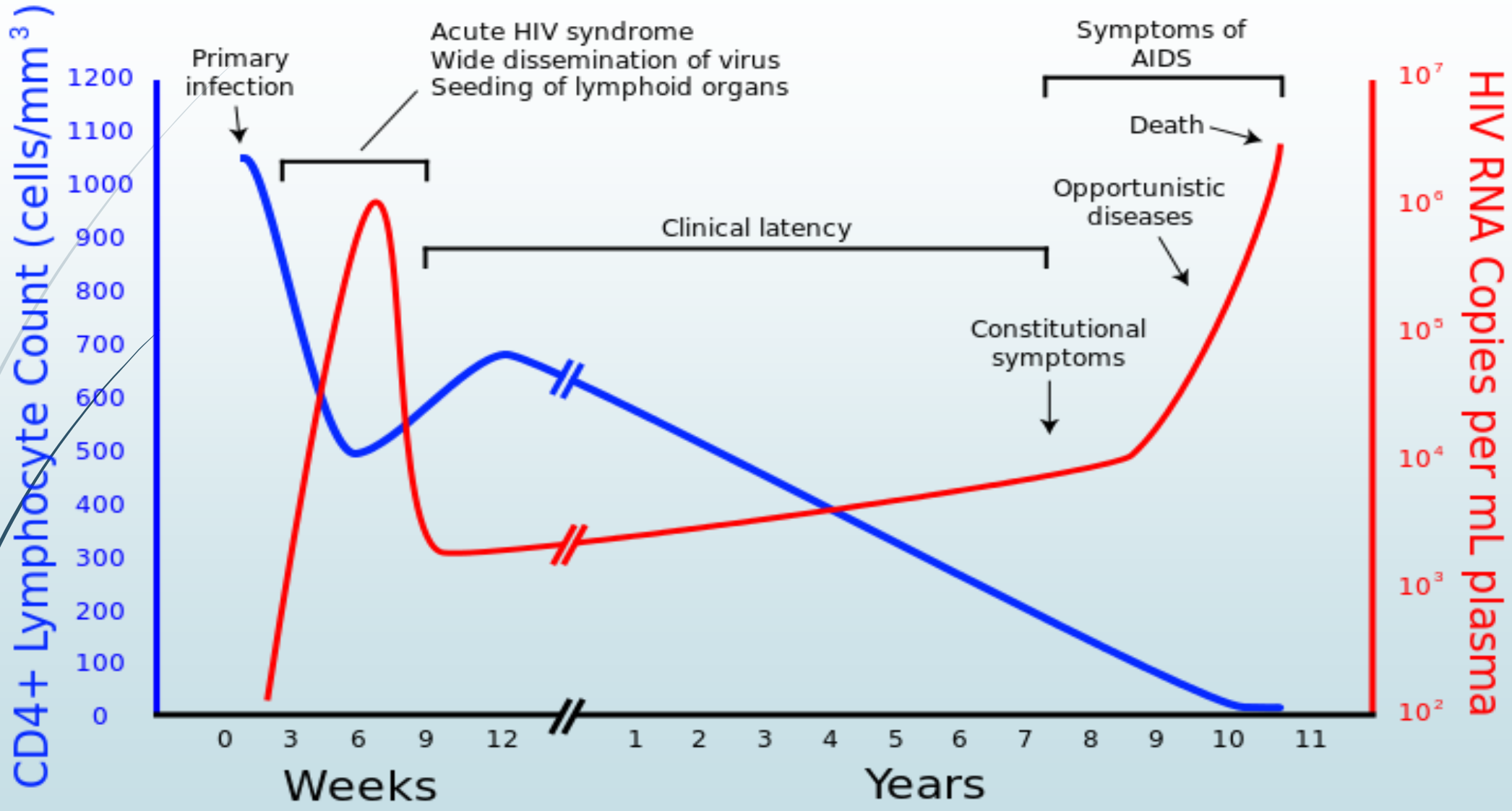
MB HIV Program, Annual Audit

Manitoba HIV Program
find. link. retain.

	2010	2011	2012	2013	2014	2015	2016	2017	2018
Male	75%	56%	63%	62%	64%	69%	68%	66%	57%
Female	25%	44%	37%	38%	36%	31%	32%	33%	40%
Transgender								4%	3%
Heterosexual	63%	67%	59%	45%	43%	33%	56%	47%	21%
Endemic	20%	5%	12%	13%	16%	21%	40%	27%	12%
MSM	22%	18%	18%	26%	30%	38%	25%	25%	24%
IDU	16%	11%	11%	11%	11%	8%	11%	18%	35%
Indigenous	38%	53%	61%	53%	45%	23%	38%	40%	51%
CD4 <200	35%	38%	41%	26%	26%	30%	26%	20%	14%
Total (N)	**102**	**80**	**56**	**89**	**87**	**102**	**103**	**95**	**115**

115 new case to care in 2018

HIV Natural History



Advances in HIV Treatment

- 1987 – AZT
- 1996 – Highly Active Antiretroviral Therapy (HAART)
- Today: combination pills – as little as one pill once daily
- Treatment recommended for all
- Chronic manageable disease
- Life Expectancy approximately 90% of general population in Canada
- Lower life expectancy for women, people who inject drugs, Aboriginal ancestry, CD4 count < 350 at time of treatment start

Life expectancy of HIV-positive individuals on combination antiretroviral therapy in Canada.
Patterson S[1,2], et al; CANOC collaboration.

Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population.
Curr Opin HIV AIDS. 2016 May 31.
Wandeler G[1], Johnson LF, Egger M.

HIV Testing Recommendations

Manitoba HIV Program
find. link. retain.

We recommend that health care providers know the HIV status of all patients under their care.

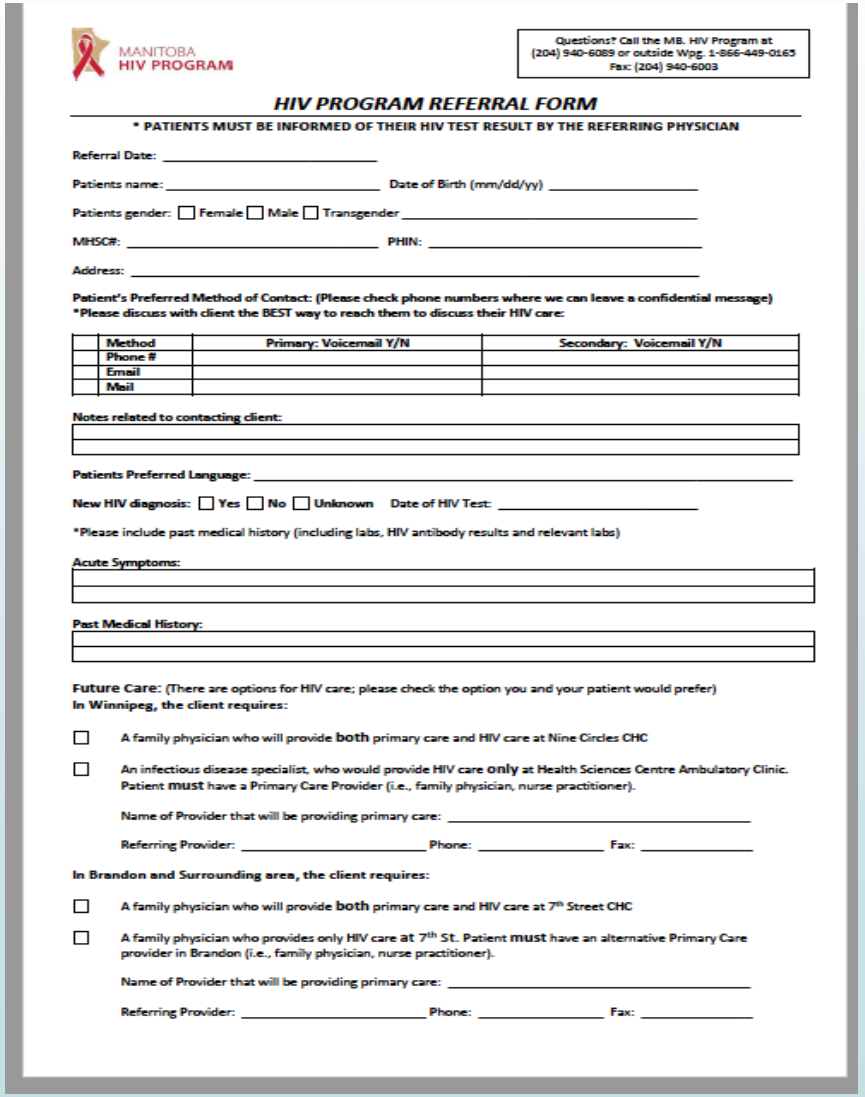
Specifically, we recommend that providers offer an HIV test

- Routinely, every five years, to all patients aged 18-70 years
- **Routinely, every year, to all patients aged 18-70 years who belong to populations with a higher burden of HIV infection**
- Once for patients older than 70 years of age, if HIV status is not known

http://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/office-of-the-provincial-health-officer/hiv-testing-guidelines-bc.pdf

BRITISH COLUMBIA | Office of the Provincial Health Officer

MB HIV Program Referral



MANITOBA HIV PROGRAM

Questions? Call the MB. HIV Program at
(204) 940-6089 or outside Wpg. 1-866-449-0165
Fax: (204) 940-6003

HIV PROGRAM REFERRAL FORM

*** PATIENTS MUST BE INFORMED OF THEIR HIV TEST RESULT BY THE REFERRING PHYSICIAN**

Referral Date: _____

Patients name: _____ Date of Birth (mm/dd/yy) _____

Patients gender: ☐ Female ☐ Male ☐ Transgender _____

MHSC#: _____ PHIN: _____

Address: _____

Patient's Preferred Method of Contact: (Please check phone numbers where we can leave a confidential message)
***Please discuss with client the BEST way to reach them to discuss their HIV care:**

	Method	Primary: Voicemail Y/N	Secondary: Voicemail Y/N
	Phone #		
	Email		
	Mail		

Notes related to contacting client:

Patients Preferred Language: _____

New HIV diagnosis: ☐ Yes ☐ No ☐ Unknown **Date of HIV Test:** _____

*Please include past medical history (including labs, HIV antibody results and relevant labs)

Acute Symptoms:

Past Medical History:

Future Care: (There are options for HIV care; please check the option you and your patient would prefer)
In Winnipeg, the client requires:

☐ A family physician who will provide **both** primary care and HIV care at Nine Circles CHC

☐ An infectious disease specialist, who would provide HIV care **only** at Health Sciences Centre Ambulatory Clinic. Patient **must** have a Primary Care Provider (i.e., family physician, nurse practitioner).

Name of Provider that will be providing primary care: _____

Referring Provider: _____ Phone: _____ Fax: _____

In Brandon and Surrounding area, the client requires:

☐ A family physician who will provide **both** primary care and HIV care at 7th Street CHC

☐ A family physician who provides only HIV care at 7th St. Patient **must** have an alternative Primary Care provider in Brandon (i.e., family physician, nurse practitioner).

Name of Provider that will be providing primary care: _____

Referring Provider: _____ Phone: _____ Fax: _____

HIV Management

Adapted from BC HIV Primary Care Guidelines	

Baseline Evaluation	• Investigations to:
	  • Assess immune system (**CD4 Count**)
	  • Rule out coinfections, opportunistic infections, and comorbidities
	  • Guide need for prophylaxis
	  • Guide treatment selection

Goals of Treatment	• Reduced morbidity, mortality & prolong duration and quality of survival • Restore and improve immunologic function • Suppress HIV Viral Load • Prevent Transmission
When to Initiate Treatment	• Treatment recommended for all • Should understand risks and benefits to adherence

http://www.cfenet.ubc.ca/guidelines/
https://aidsinfo.nih.gov/guidelines
http://www.eacsociety.org/files/guidelines_9.0-english.pdf

Prophylaxis against Opportunistic Infections

CASE: CD4 count was 175 (13%) cells/ml, initiated prophylaxis with Septra SS one tab once daily

- <200 (15%) Pneumocystis Jirovecii Pneumonia (PJP) prophylaxis
  - Sulfamethoxazole/Trimethoprim. DS or SS 1 tab once daily OR
  - Dapsone 100 mg once daily

- <100 (10%) Toxoplasmosis prophylaxis (if Ab+)
  - Sulfamethoxazole/Trimethoprim DS 1 tab once daily

- <50 (5%) Mycobacterium Avium Intracellulare (MAI) prophylaxis
  - Azithromycin 1200 mg q weekly OR
  - 600 mg 2x/wk OR Azithromycin 250 mg 5x/wk

HIV Treatment - Antiretroviral Therapy (ART)

ART= 3 drugs from 2 classes

Backbone of 2 drugs, 1 Class	Plus Additional 1 drug, different class
2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	1 Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI), OR
	1 Protease Inhibitor (PI), OR
	1 Integrase Inhibitor

Treatment Guidelines:
https://aidsinfo.nih.gov/guidelines
https://www.iasusa.org/wp-content/uploads/guidelines/arv/arv_2018.pdf
http://www.eacsociety.org/files/guidelines_9.0-english.pdf

OAT improves Treatment Uptake and Outcomes

- People who use drugs are less likely to receive antiretroviral therapy (ART)
- Good evidence OAT with buprenorphine or methadone:
  - Increases retention in care
  - Increases ART uptake
  - Improves ART adherence
  - Increased viral suppression

Curr Opin Infect Dis. 2015 Feb;28(1):10-6. doi: 10.1097/QCO.0000000000000125.

Challenges in managing HIV in people who use drugs.

Kamarulzaman A[1], Altice FL.

Author information

EDITOR'S CHOICE

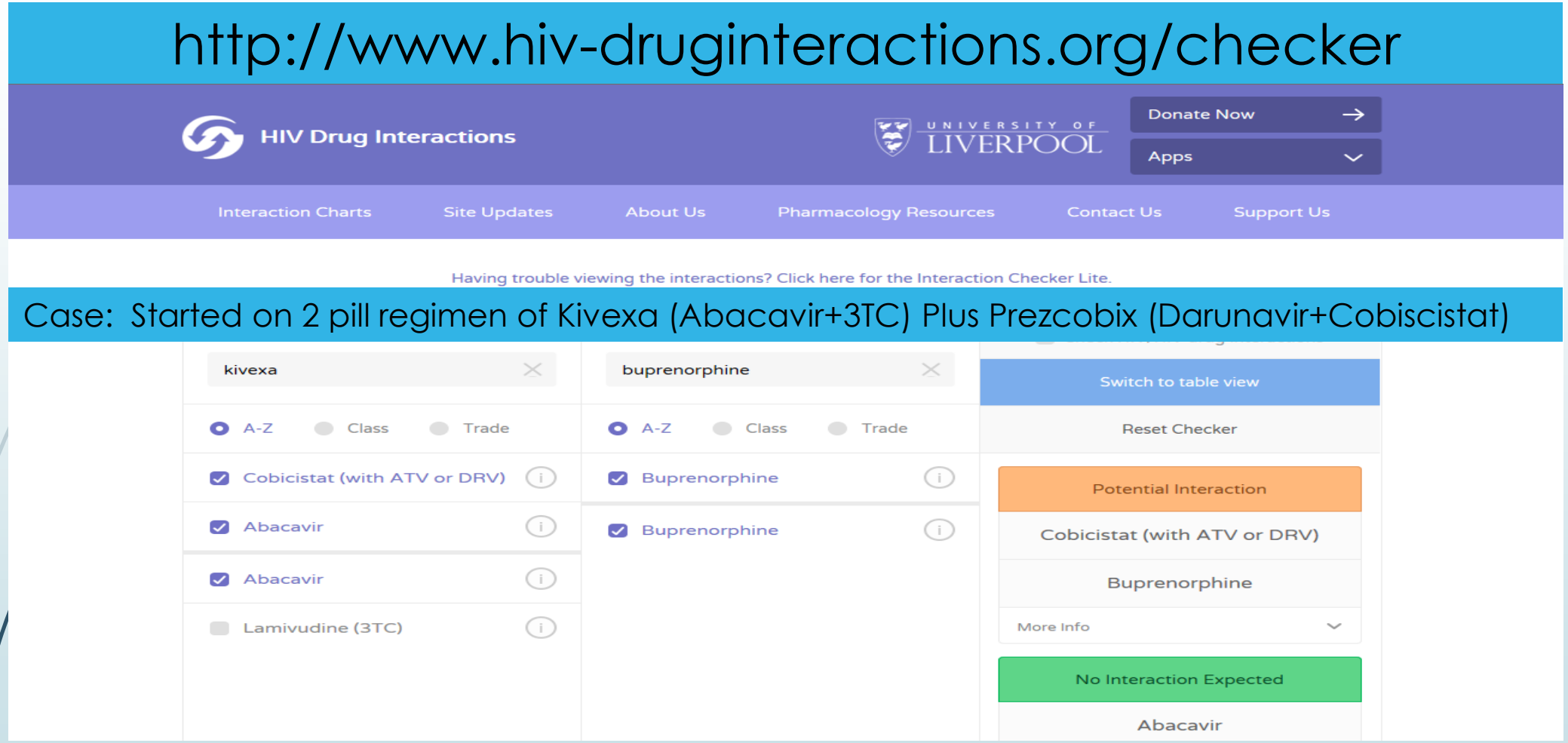
Impact of Opioid Substitution Therapy on Antiretroviral Therapy Outcomes: A Systematic Review and Meta-Analysis

Andrea J. Low, Gitau Mburu, Nicky J. Welton, Margaret T. May, Charlotte F. Davies, Clare French, Katy M. Turner, Katharine J. Looker, Hannah Christensen, Susie McLean, Tim Rhodes, Lucy Platt, Matthew Hickman, Andy Guise, Peter Vickerman

Clinical Infectious Diseases, Volume 63, Issue 8, 15 October 2016, Pages 1094–1104, https://doi-org.uml.idm.oclc.org/10.1093/cid/ciw416

Drug-Drug Interactions

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



Case: Started on 2 pill regimen of Kivexa (Abacavir+3TC) Plus Prezcobix (Darunavir+Cobiscistat)

MB HIV Program Pharmacist: Pager: 204-932-1100
Available for consultation for persons living with HIV in MB

Description of the interactions

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

Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Darunavir + Buprenorphine
Coadministration of buprenorphine/naloxone and twice daily darunavir/ritonavir had no significant effect on buprenorphine or naloxone, but increased concentrations of norbuprenorphine. Coadministration with once daily darunavir/ritonavir produced no significant changes in the pharmacokinetics of buprenorphine or norbuprenorphine, but increased concentrations of the inactive buprenorphine-3-glucuronide. The clinical relevance of the increase in norbuprenorphine concentrations has not been established. Dose adjustment for buprenorphine may not be necessary but careful clinical monitoring for opiate toxicity is recommended.

Cobicistat (with ATV or DRV) + Buprenorphine
Coadministration of buprenorphine/naloxone and cobicistat increased buprenorphine AUC, Cmax and Cmin by 35%, 12% and 66%, respectively, whereas naloxone exposure was modestly reduced (AUC and Cmax both decreased by 28%). The European SPC advises that no dose adjustment of buprenorphine is required when coadministered with cobicistat, but the US Prescribing Information suggests careful dose titration when initiating buprenorphine and advises a dose adjustment of buprenorphine may be needed when starting cobicistat.

Case: Cobicistat may increase buprenorphine levels – dose adjustment may be needed

HIV Follow-up Monitoring

- Repeat labs 1 month after treatment start, Then q 3-6 months
- Closer follow up for OAT monitoring
- Adherence
- New meds, review for Drug-drug interactions
  - Antacids, Erectile dysfunction medications, Anticonvulsants, Inhaled corticosteroids, OCPs
- Discuss transmission risks, sexual activity, drug use, disclosure if risks for transmission
- Reproductive health/contraceptive needs
- BW Monitoring : CD4 and Viral Load, CBC, lytes, creat, LE, U/A, U ACR
- Regular STBBI screening, annually or more frequently guided by risk activity, including oral and rectal swabs
- Annual cervical ca screening, DM screen and CVD screening with lipid profile, immunizations

HIV Primary Care Guidelines available at: http://www.cfenet.ubc.ca/guidelines/

Helena

- Started Prezcobix (Darunavir/cobicistat) and Kivexa (Abacavir/3TC) daily administered alongside buprenorphine/naloxone at community pharmacy
- No dose adjustment was needed
- HIV viral load suppressed at < 20 copies/ml within 3 months
- CD4 rises to 450 cells/mm3
- Remains stable for over ~2 years on ART with suppressed viral load with no opiate or other drug use
- Then more frequent DNA appointments in clinic
- Urine +amphetamines, and disclosing active IDU
- + Hepatitis C AB, + Core antigen

Hepatitis C

- RNA Flavivirus
- 6 Major genotypes, Genotype 1 accounts for 60% of cases in Canada
- IDU is main mode of Hepatitis C transmission (80% of new infections)
- Infects liver, leads to progressive liver disease
- 25% will clear the virus, 75% will progress to chronic Infection
  - 10-15% will develop cirrhosis
  - 2-4 % will develop liver failure or hepatocellular carcinoma
- Treatment can cure disease

Hepatitis C Epidemiology

- 170 million people living with hepatitis C worldwide in 2014
- 500,000 die of hepatitis C-related liver disease every year
- Approximately 250,000 people living with Hepatitis C in Canada
- Approximately 44% are unaware of their infection
- In MB 616 case in 2017, > 700 in 2018

Canadian Liver Foundation @: http://www.liver.ca/liver-disease/types/viral_hepatitis/Hepatitis_C.aspx

Hepatitis C Testing Recommendations

Population Based Screening

- Born between 1945-1975

Risk-Based Screening:

- Current or past injection drug use
- Received health care or personal services where lack of infection prevention and control practices
- Blood transfusion, blood products or organ transplant before 1992 in Canada
- History of incarceration
- Born or resided in a region where hepatitis C prevalence is > 3%,
- Born to a mother who is HCV-infected
- History of sexual contact or sharing personal care items with someone HCV-infected
- HIV infection, particularly men who have sex with men
- Chronic hemodialysis treatment
- Elevated alanine aminotransferase

http://www.hepatology.ca/

Hepatitis C Management

The management of chronic hepatitis C: 2018 guideline update from the Canadian Association for the Study of the Liver

Hemant Shah, Marc Bilodeau, Kelly W. Burak, Curtis Cooper, Marina Klein, Alnoor Ramji, Dan Smyth and Jordan J. Feld; for the Canadian Association for the Study of the Liver

CMAJ June 04, 2018 190 (22) E677-E687; DOI: https://doi.org/10.1503/cmaj.170453

Adapted from the 2018 Canadian Guidelines on the Management of Hepatitis C	

Baseline Assessment	• Investigations to:
	  • Assess extent liver disease
	  • Rule out coinfections, other forms liver disease
	  • Guide treatment selection

Goals of Treatment	• Cure • Prevent Transmission • Reduced morbidity, mortality & prolong duration and quality of survival
When to Initiate Treatment	• Treatment recommended for all

Suggested work-up before beginning HCV therapy

Category	Investigation	Considerations
Routine bloodwork	• Complete blood count • Liver enzymes (alanine transaminase, aspartate transaminase, alkaline phosphatase) • Liver function (bilirubin, INR, albumin) • Creatinine	• Low platelets and elevated bilirubin or INR are suggestive of cirrhosis • Renal function is important to determine safety of some regimens
Serology to exclude other infections	• HIV • Hepatitis B (HBsAg, anti-HBs, anti-HBc)	• If HIV-positive, treatment for HIV must take drug interactions into consideration • If HBsAg-positive or anti-HBc-positive, see section on HBV coinfection (risk of HBV reactivation) (Appendix 1)
Serology to exclude other common liver diseases	• Transferrin saturation (hemochromatosis) • IgG	• Elevated immunoglobulin G may reflect cirrhosis or possibly autoimmune hepatitis
Staging of liver disease	• APRI* • FibroTest (serum panel)† • Ultrasound* • Transient elastography†	• All persons with HCV must have evaluation of fibrosis to exclude cirrhosis. • Normal ultrasound does not exclude cirrhosis.[21] • APRI < 0.7 has a very high negative predictive value to exclude cirrhosis[22]
HCV-specific	• HCV genotype and HCV RNA • Resistance testing (may be useful in select circumstances)	• To select appropriate regimen, and consideration for addition of ribavirin.

Note: anti-HBc = hepatitis B core antibody, anti-HBs = hepatitis B surface antibody, APRI = Aspartate Aminotransferase to Patelet Ratio Index, HBsAg = hepatitis B virus surface antigen, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IgG = immunoglobulin G, INR = international normalized ratio.
*All persons with HCV should have a baseline ultrasound and evaluation of fibrosis.
†Where available, use noninvasive technologies (e.g., transient elastography [FIbroscan], shear-wave elastography, MR-Elastography, or FibroTest).

Hemant Shah et al. CMAJ 2018;190:E677-E687

CMAJ·JAMC

Health Canada–approved direct-acting antiviral regimens.

Regimen	Genotype	Pills per day	Duration (wk)	Comments
Genotype-specific treatment regimens				
Elbasvir/grazoprevir (Zepatier)	1a, 1b, 4	1	12–16	Resistance testing recommended before use in genotype 1a
Ledipasvir/sofosbuvir (Harvoni)	1a, 1b, 4, 5, 6	1	8–24	
Paritaprevir/ritonavir/ombitasvir + dasabuvir (Holkira Pak)	1, 1b	4	8–24	Ribavirin must be added for genotype 1a
Paritaprevir/ritonavir/ombitasvir (Technivie)	4	2	12	Ribavirin must be added
Sofosbuvir + daclatasvir (Sovaldi + Daklinza)	1a, 1b, 3	2	12–24	
Pan-genotypic regimens				
Glecaprevir/pibrentasvir (Maviret)	1–6	3	8–16	
Sofosbuvir/velpatasvir (Epclusa)	1–6	1	12	
Sofosbuvir/velpatasvir/ voxilaprevir (Vosevi)	1–6	1	12	Approved only for direct-acting antiviral agent failures

Hemant Shah et al. CMAJ 2018;190:E677-E687

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Hepatitis C Treatment - Cure

Direct Acting Agents (DAAs) now on Manitoba Formulary:

- Harvoni (Ledipasvir/Sofosbuvir) – Genotype 1
- Sovaldi (Sofosbuvir) - Genotype 2, 3 (used with Ribavirin or Daclatasvir/Sofosbuvir)
- Epclusa (Velpatasvir/Sofosbuvir) – Genotype 1, 2, 3, 4, 5, 6
- Daclinza (Daclatasvir/Sofosbuvir) – Genotype 3 (used with Sofosbuvir)
- Zepatier (Elbasvir/Grazoprevir) – Genotype 1, 4
- **Vosevi (Sofosbuvir/Velpastasvir/Volilaprevir - Genotype 1, 2, 3, 4, 5, 6**
- **Maviret (Glecaprevir/Pibrentasvir - Genotype 1, 2, 3, 4, 5, 6**

Criteria:

- **Prescribed by a hepatologist, gastroenterologist, or infectious disease specialist**
- **Laboratory confirmed Hepatitis C genotype 1,2,3,4,5,6 or mixed genotype**
- **Quantitative Hepatitis C RNA viral load level within last 6 months**

>90, up to 99% Cure Rates with DAAs

Hepatitis C Treatment for PWID

- Recent or active IDU should not be seen as an absolute contraindication to HCV therapy.
- Strong evidence from various settings in which persons who inject drugs have demonstrated adherence to treatment and low rates of reinfection, countering arguments that have been commonly used to limit treatment access in this patient population
- Ideally, treatment of HCV-infected persons who inject drugs should be delivered in a multidisciplinary care setting
- Combining HCV treatment with supply distribution and opioid agonist therapy programs in this population has shown great value in decreasing the burden of HCV disease.

Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals

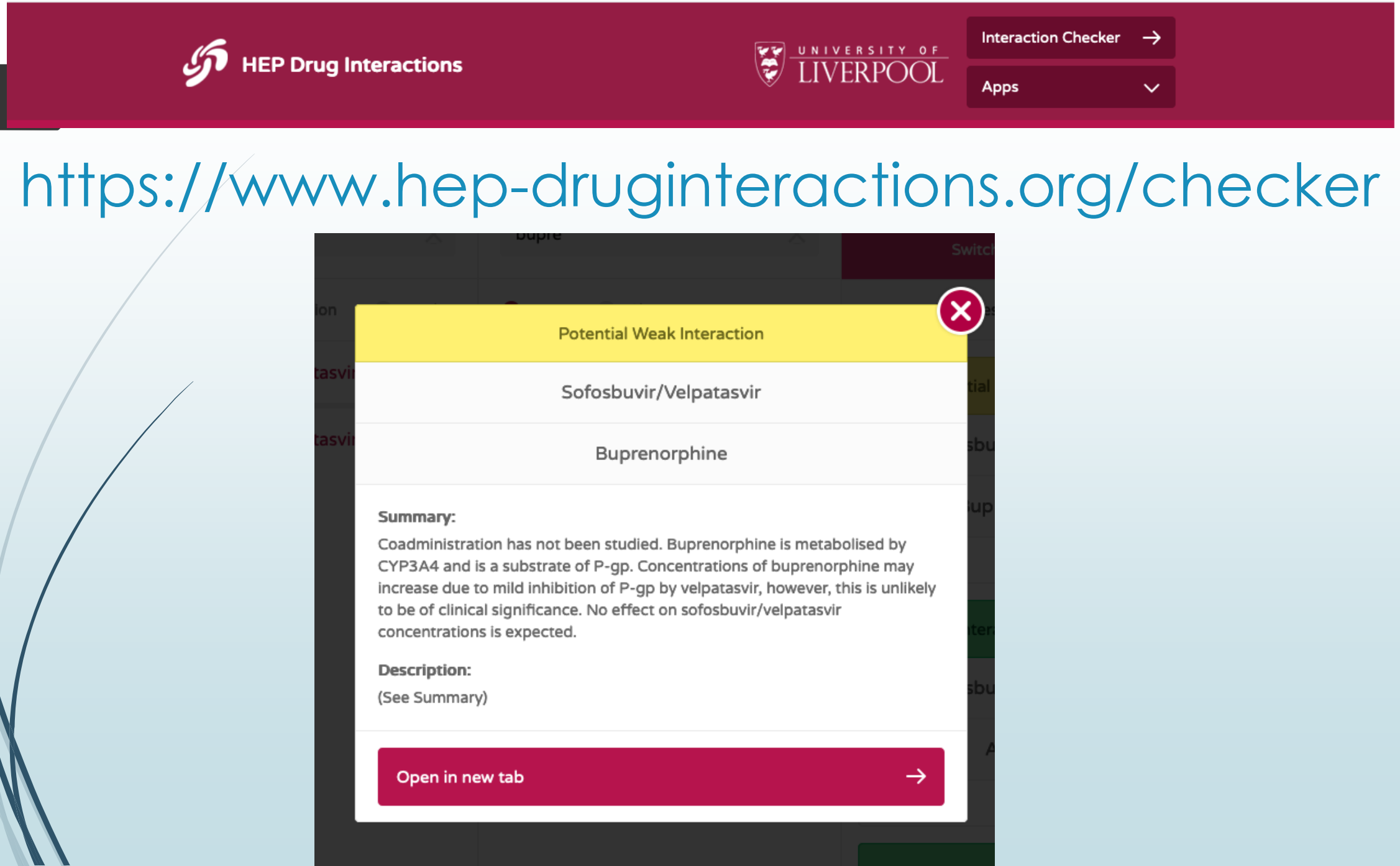
Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. **Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals.** Hepatology. 2013;58(5):1598-1609.

Hepatitis C Treatment in MB

- Viral Hepatitis Investigative Unit, HSC, Ph: 204-787-3630, Fax 204-787-7086
- Mount Carmel Clinic, Ph: 204-589-9428, Fax: 204-582-6006
- eConsult Hepatology – Hepatitis C Treatment advice
  - Email mbeconsult@umanitoba.ca to register

Helena

- Hepatology recommended Hepatitis C Treatment with with Epclusa (Velpatasvir/Sofosbuvir) and reviewed by HIV Pharmacist for any drug-drug interactions
- Expect cure with12 weeks of treatment



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

Prevention HIV and Hepatitis C

- Condoms
- Supply distribution
- Addictions Treatment
- Opiate Agonist Therapy
- Antiviral based interventions
  - ART to prevent onward transmission HIV
  - Hep C treatment to prevent onward transmission Hep C
  - PrEP for prevention new infection in HIV negative at high risk
    - Tenofovir DF + Emtricitabine (Truvada) i tab once daily
    - Not covered by MB pharmacare, covered by FNIHB, ~ $250/month
    - Guidelines for use http://www.cmaj.ca/content/189/47/E1448
    - Assessments for PrEP done at Nine Circles testing clinic 5 days/week

Summary

- Test for HIV and Hepatitis C and other Sexually Transmitted Infections
- Rescreen at risk populations annually or more frequently if high risk
- PWUD do well on antiretroviral therapy for HIV
- Opiate agonist therapy improves engagement in care, adherence to treatment and outcomes for people with opioid use disorder and HIV
- Hepatitis C can be cured and treatment should be offered to all people who qualify including PWUD/ PWID and those on ORT
- Drug-Drug interactions may be significant and expert consultation is available

References and Resources:

http://education.cfenet.ubc.ca/bc-cfe-guidelines/

http://www.catie.ca/

http://www.cdc.gov/

http://hcvguidelines.org/full-report-view

http://liver.ca/liver-disease/types/viral_hepatitis/Hepatitis_C.aspx

http://www.hepatology.ca/

Thank You

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