Land Acknowledgement

- *We would like to begin by acknowledging that we are on the traditional lands, referred to as Treaty 6 Territory and that the participants of this session, and all the people here, are beneficiaries of this peace and friendship treaty.*

- *Treaty 6 encompasses the traditional territories of numerous western Canadian First Nations, including Cree, Dene, Stoney Nakota Sioux, Saulteaux, and Ojibwe.*

Reminder:

This videoconference/webinar will be recorded

3HP - Reimplementation of Rifapentine for the Treatment of Latent TB Infection

October 2022

First Nations and Inuit Health Branch (FNIHB) - Alberta Region

Today's session will cover

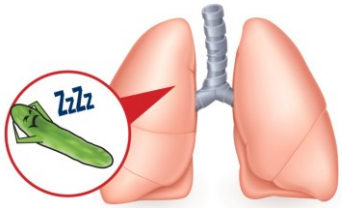
- TB Infection vs TB disease

- Treatment of LTBI
  - review LTBI treatment options
  - rifapentine: what it is and how it is used in latent TB infection (LTBI) treatment

- How Rifapentine is used to treat LTBI in Canada
  - when it started, why it ceased and why its being resumed
  - rifapentine and the nitrosamine impurity present in current supply
  - talking to patients about 3HP treatment for LTBI

TB Infection vs. TB Disease

- **TB Infection (Latent TB Infection-LTBI):** TB bacteria are DORMANT (asleep) in the body so the person is not sick and cannot pass the bacteria to others.



- Healthy person
- Macrophages engulf the organism
- No symptoms
- Germs present but dormant
- Cannot be spread to others
- Germs can remain dormant for decades

- **TB Disease (active TB):** TB bacteria are ACTIVE (awake) in the body so the person is sick with symptoms and can pass the bacteria on to others.
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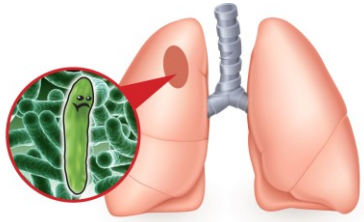

- Depressed immune system
- Macrophages fail & germs 'wake' up
- Can occur quickly (weeks or months)
- Can occur slowly (years after infection)
- Greatest risk in first 2 years after infection
- Some factors/conditions increase this risk

Treatment of TB

- TB Medications can be taken to treat both active TB disease and latent TB Infection

Treatment of active TB disease:

– The TB bacterial are awake and causing illness (can also possibly be spread to others).

– Medication is needed to kill the TB bacteria to provide cure for the patient and prevent any spread of TB.

Treatment of LTBI (preventative therapy):

– Kill the TB bacteria while it is in its dormant state so the bacteria doesn't have the chance to wake up and turn in to active TB disease for the client in the future.

– Treatment for LTBI prevents future cases of TB, and prevents future spread of TB to others.

Preventative Therapy (Treatment for LTBI)

- Treatment of LTBI is an effective TB prevention strategy and an important step towards TB elimination
- There is an abundance of evidence on the effectiveness of preventative therapy in high-risk individuals; proof of the population-level effect of preventative therapy also exists in many settings across the world
- Preventative therapy yields significant health and cost benefits both in the short and long term

Preventative Therapy (treatment for LTBI)

- There are many treatment options available for treating latent TB infection
- In recent years, **a key breakthrough in the <u>prevention</u> of active TB disease has been the introduction of 3HP** (**rifapentine used in combination with INH**) as an acceptable alternative treatment for LTBI

Medication	Frequency	Duration	Doses required to complete	Max time interval to complete
Isoniazid (INH)	daily	9 months	270	12 months
Isoniazid (INH)	2x/week	9 months	78	12 months
Isoniazid (INH) & Rifampin (RMP)	2x/week	4 months	35	6 months
Isoniazid (INH) & Rifampin (RMP)	daily	3-4 months	90-120	4.5 - 6 months
Rifampin (RMP)	daily	4 months	120	6 months
Rifampin (RMP)	5x/week	4 months	85	6 months
Rifapentine (RPT) & Isoniazid (INH)	**once/week**	**12 weeks**	**12**	**16 weeks**

Preventative Therapy (Treatment for LTBI)

3HP:

- has been shown to be as effective as the standard treatment of 9 months of INH monotherapy while demonstrating higher treatment completion rates
- constitutes a major advance in treating persons with LTBI and contributing to the control of active TB disease, particularly in high-income, low-incidence countries (like Canada)
- has become a preferred treatment for LTBI in many communities facing recurrent outbreaks of active TB disease resulting from ongoing community transmission

What is Rifapentine?

- Often called RPT for short
- Belongs to a class of drugs called antitubercular agents
- Is a rifamycin derivative; is an antimicrobial with a similar profile of microbiological activity to Rifampicin (Rifampin)
- Manufactured by Sanofi; brand name is Priftin
- Supplied as 150 mg round, normal convex dark pink film-coated tablets debossed with ‘Priftin’ on one side and ‘150’ on the other side
- Stored at 15-30 degree Celsius (protect from excess heat and humidity)
- Give with meals (increases its bioavailability)

How is Rifapentine used?

- dosage determined by weight, up to a maximum dosage of 900mg (usually more tablets than rifampin dose)
- globally, uses include treating active bacterial infections and latent TB infection
- in Canada, approved only for the treatment of LTBI in combination with Isoniazid (INH) and vitamin B6 (3HP).
- Given as DOT

How is Rifapentine used?

Pros:

- given only once a week x 12 weeks (12 doses)
- shorter duration: easier to give, easier to take and easier to successfully complete

Cons:

- increased monitoring/reporting is required compared to other LTBI treatment regimens
- additional reporting required because of access process
- surveillance for rare hypersensitivity reaction that can occur
- contraindicated in pregnant women/those trying to become pregnant, breastfeeding women, HIV clients on select antiretroviral therapy (ARVs) and children under 2 years of age
- more tablets than Rifampin/INH regimen (per dose)
- theoretical risk of cancer related to an impurity detected in the currently available medication supply*

* More to come on this

LTBI Treatment with 3HP

Examples of 3HP dosages based on weight

Patient	Rifapentine (RPT)	INH	Vitamin B6
Adults > 50 kg	900mg weekly DOT	15mg/kg up to a max of 900mg weekly DOT	50mg DOT weekly
Adults 30-50 kg	750mg weekly DOT	15mg/kg up to a max of 900mg weekly DOT	50mg DOT weekly
Children > 2 years old	Per chart monograph weekly DOT	25mg/kg up to a max of 900mg weekly DOT	25mg weekly DOT
Children < 2 years old	Contraindicated	-	-

LTBI Treatment with 3HP

Visual example of what 900mg (max dose) of RPT looks like	Visual example of what 900mg (max dose) of INH and 50mg of vitamin B6 looks like
	

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LTBI Treatment with 3HP

- completion means taking 12 doses within 16 weeks
- doses to be given 7 days apart BUT if need to catch up on a missed dose, must be at lest 3 days between doses and no more than 5 doses in a 30 day period
- Anyone prescribed 3HP to treat LTBI requires teaching and/or assessments at:
  1. **baseline**
  2. **weekly, with each dose**
  3. **monthly**
  4. **other (i.e., compliance reporting to TB Services)**

LTBI Treatment with 3HP

Baseline assessment, pre-medication teaching and documentation:

- patient medical history including allergies and pregnancy/breastfeeding status
- current medication list to ensure no drug interactions (verify list with pharmacy and send to TB Services)
- current weight
- baseline bloodwork (ALT, total bilirubin, and CDC-diff)
- inform on the theoretical increased risk of cancer due to impurity in RPT
- inform that it can reduce effectiveness of other medications (i.e., birth control)
- monitoring requirements (how often, how long, missing doses, bloodwork, etc.)
- take with food
- processed through the liver: avoid/limit alcohol and acetaminophen use
- possible side effects, including *'hypersensitivity reaction'* (what it is, what to look for, reporting)
- common interactions (medication and others)

LTBI Treatment with 3HP

Baseline assessment, pre-medication teaching and documentation (cont'd):

- possible common drug-drug interactions with RPT (can speed up the removal of other medications from the body making them less effective):

- Oral contraception (alternative forms of birth control required) - Coumadin and other anticoagulants / blood thinners	- Calcium channel blockers - Digoxin - Asunaprevir - Phenytoin	- Ranolazine - Tacrolimus - Suboxone, oxycodone & methandone	- Antiretroviral & certain HIV medications - AEDs - more….

- RPT may interfere with certain laboratory tests (i.e., folate and vitamin B12)

- INH may interfere with Phenytoin (Dilantin) (anti-seizure med) and thus levels should be monitored by family physician more often

LTBI Treatment with 3HP

Baseline assessment, pre-medication teaching and documentation (cont'd):

Potential side effects of 3 HP	
Rifapentine (RPT)	**Isoniazid (INH)**
• GI upset • Rash • Hepatitis • *'Hypersensitivity Reaction'* generally characterized as flu like symptoms and/or especially fever/chills, wheezing/bronchospasms/shortness of breath, hives/urticaria, swollen lips/angioedema, watery eyes/conjunctivitis • possible staining of skin, tears, sweat, saliva, urine, or stools with impact to dentures and contact lenses, etc.	• Hepatitis • Peripheral neuropathy (vitamin B6)

LTBI Treatment with 3HP

Weekly monitoring to be completed prior to each dose given:

- general inquiry as to clients feelings of well-being
- complete DOT checklist: If yes to any symptoms marked with an asterisk (*)
    - *HOLD dose*
    - *Complete assessment with the patient (i.e., when symptoms started, how long they lasted, details of what is being reported, etc.).*
    - *Notify TB Services and follow their direction for next steps*
      - symptoms of '*hypersensitivity reaction*' generally occur 3-4 hours after dose (should not experience symptoms days after dose)
      - < 5% should ever need to stop the medications
      - liver inflammation and allergic reactions are very rare
- verify no changes/additions to medications

LTBI Treatment with 3HP

Monthly requirements:

- **patient:**
  - bloodwork (ALT, total Bili, and CBC-diff)
- **nursing assessment for:**
  - tolerability
  - drug interactions (sooner if client starts a new medication)
  - weight

The above may need to be done more often if clinically indicated.

LTBI Treatment with 3HP

Other required reporting:

- **medication compliance reporting to TB Services:**
  - after completion of first month of medications and again at the end of treatment (unless otherwise indicated)
  - notify TB Services if client misses 2 doses - to ensure client will be able to complete on time
- **adverse events reporting to TB Services:**
  - because of how this medication is accessed TB Services is required to do additional reporting on RPT when there are any side effects or hypersensitivity reactions
  - any side effects and especially those marred with an asterisk (*) on the DOT checklist, should be reported to TB Services for the TB physician to determine if the side effect should be considered an adverse event and reported

Rifapentine in Canada

Rifapentine has never been authorized for use in Canada through regular processes

- not because it isn't a safe mediation; not being approved for use in Canada has nothing to do with the utility or safety of the medication
- drug approval processes are long, cumbersome and costly
- often certain medications are not marketed in Canada for reasons related to business decisions by the manufacturer due to small market size
  - often not worth costs associated with the approval process
  - manufacturer's focus on pursuing the authorization process for medications that are new and/or will be utilized on a large scale (worth the time and expense)

Rifapentine is approved for and actively in use in the United States to treat both LTBI as well as active TB disease.

Rifapentine in Canada

Before 2018

- Rifapentine could only be accessed though Canada's *"Special Access Program"* (SAP)
  - a long, cumbersome and patient specific program

Early 2018

- Rifapentine was added to the *'List of Drugs for an Urgent Public Health Need"* under the "Access to Drugs in Exceptional Circumstances" making it easier to access (but still not approved through the regular processes)
  - division 10 of the Food and Drug Regulations called 'Access to Drugs in Exceptional Circumstances", enables access to drugs not available in Canada but that are authorized for sale in certain other foreign jurisdictions in order to address urgent public health needs or public health events that are occurring/require immediate action
  - rifapentine was added to the '*List of Drugs for an Urgent Public Health Need"* for treating LTBI

Summer 2018

- The Alberta TB Program began accessing Rifapentine under the '*Access to Drugs in Exceptional Circumstances'* program for LTBI treatment with 3HP

Rifapentine in Canada

June 2020

- Sanofi alerted health agencies and stakeholders about a newly detected impurity in Priftin (rifapentine), 1-cyclopentyl-4-nitrosopiperazine (CPNP), a potential carcinogen
- Health Canada released statement that they had been made aware of CPNP in Priftin (rifapentine)
  - Sanofi began root-cause investigation to determine the source of the impurity
  - No patient adverse events were noted or reported
  - Sanofi put a hold on producing rifapentine
  - Sanofi committed to updating Canada on further testing in production facilities and market-ready medications by the end of July 2020
  - Decision made for those already on rifapentine to continue it until completion but no new LTBI treatment was to occur until further notice

Rifapentine in Canada

July 2020

- Alberta TBS and FNIHB advises that rifapentine will not be used until further notice/more information is available (those currently on treatment were allowed to complete their course)

October 2020 to January 2021

- US FDA advises they are not objecting to rifapentine with CPNP at or below 20 ppm given the benefit of taking it outweighs any theoretical risk the impurities pose
- PHAC, ISC and Health Canada begin working to align approaches with the US FDA
- PHAC and ISC conducts risk/benefit assessment, consulting TB experts/ clinicians (who express the importance of the medication to treat LTBI)

Rifapentine in Canada

March 2021

- acceptable concentration limit of nitrosamine impurity CPNP is normally less than 0.11 ppm
- rifapentine currently available contains CPNP impurity levels between 12 ppm - 25 ppm
- Canada increased the interim acceptable limit to less than or equal to 20 ppm at release and less than or equal to 25 ppm at the end of shelf life
- interim acceptable limit to remain in effect until Sanofi reduces the CPNP to less than 0.11 ppm
- Sanofi commits to test all lots prior to release to the Canadian market
- Canada continues to monitor progress and expects Sanofi to reduce the levels as soon as possible

Rifapentine in Canada

March 2021 continued…

- use of rifapentine for treating LTBI based on interim acceptable limits resumes in situations where there is a high risk of non-adherence or non-completion of treatment, or where other treatment alternatives are not feasible or suitable
- clients need to be informed on the impurity that exists in the current stock of rifapentine, the theoretical risk of cancer associated with taking rifapentine and other options available to them so that they can make an informed decision to take it or not

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Dr. Ryan Cooper, Medical Director TB Services

- *What are nitrosamines?*
- *What are the nitrosamines found in Rifapentine?*
- *What is the benefit vs risk of taking rifapentine containing nitrosamine impurities to treat LTBI?*
- *Resuming the use of 3HP to treat LTBI.*

What are Nitrosamines?

Nitrosamines (*ni·TRO·sa·meens) are:*

- organic compounds; there are many different types; they have no known industrial use
- are unintentional by-products formed during food preparation/processing and when chemical reactions occur during medication manufacturing
- based on animal studies, nitrosamine impurities are classified as probable or possible human carcinogens
- are not expected to cause harm at very low levels, but when someone is exposed to higher levels over a long period of time, they could have a slightly higher risk of cancer
- long-term exposure to a level above what is considered safe could increase the risk of cancer

What are Nitrosamines?

- We are all exposed to some level of nitrosamine every day
- Low levels of nitrosamines are all around us and are in many consumer products
  - food (i.e., processed and cured meats, some other foods such as some fish, fried foods, vegetables, diary products like non-fat milk and some cheeses, alcoholic beverages like beer);
  - Water (found naturally);
  - consumer products such as some medications (ie., some used treat HTN, acid reflux), cosmetics, tobacco products, and cigarette smoke; and,
  - the environment (air pollution)
- At low levels, nitrosamines are not expected to cause harm
- There are may types of Nitrosamines

What are the Risks Associated with Nitrosamines?

- There is no immediate health risk associated with the use of medications containing low levels of a nitrosamine impurity
- It is not expected that a nitrosamine impurity will cause harm when exposure is at or below the acceptable level
  - i.e., no increase in the risk of cancer is expected if exposure to the nitrosamine impurity remains below the acceptable level, even if it occurs every day for 70 years
- Actual health risk varies from person to person and depends on several factors such as the daily dose of the medication, how long the medication is taken for and the level of the nitrosamine impurity in the finished product
- Not treating a condition may pose a greater health risk than the potential exposure to a nitrosamine impurity

What are the Nitrosamines found in Rifapentine?

- The unwanted molecules (impurity) formed when rifapentine is made is scientifically known as 1-cyclopentyl-4-nitrosopiperazine (CPNP)
- Limited information is available on CPNP (the type of Nitrosamine currently in rifapentine)
- CPNP belongs to the nitrosamine class of compounds some of which are classified as potential carcinogens
  - Similar to other nitrosamine impurities, CPNP is expected to exhibit mutagenic and carcinogenic activity
  - CPNP itself has not been shown to cause cancer in people or animals, however it is like other nitrosamines that have caused cancer in people. It was also shown to cause gene mutations in a lab study.
- The rifapentine available in Canada has higher levels of nitrosamine that what is considered acceptable
- Experts have estimated the possible risks of CPNP using information available on similar nitrosamines.

What are the benefits vs risks associated with taking Rifapentine (as part of the 3HP regimen) for treatment of LTBI?

Benefits:

- 3HP is a much shorter treatment given less frequently compared to other latent TB treatment options, making it easier for many patients to complete
  - taken only once weekly for 3 months, other treatment options can last up to 9 months and are take more frequently
  - longer/more frequent dosing make treatment hard to complete for some people, so for these individuals, the benefit of taking 3HP may outweigh any potential health risks associated with CPNP
- 3HP is as effective as the standard 9 month treatment and more people successfully complete 3HP compared to other regimens

What are the benefits vs risks associated with taking Rifapentine (as part of the 3HP regimen) for treatment of LTBI?

Risks:

- A theoretical risk of developing cancer exists related to taking rifapentine
  - Health Canada estimates that up to 1 out of 34,000 patients exposed to this nitrosamine may develop cancer
  - on average, everyone already has a nearly 1 in 2 chance of developing cancer in their lifetime (even without taking rifapentine)

Resuming the use of rifapentine (3HP Regimen) to treat LTBI

- Canadian TB experts have weighed the potential risks related to the nitrosamine impurity found in rifapentine against the known benefits of using rifapentine to treat latent TB infection
- Canadian TB experts recommended that rifapentine remain available as a treatment option to Canadians and still recommend considering rifapentine as a treatment option for LTBI
  - TB is a potential deadly disease that affects the lungs and sometimes other parts of the body
  - TB is treatable and curable but permanent damage to the body and sometimes death from TB still occurs
  - 1 in 10 persons with LTBI will develop TB disease without treatment (higher in those with medical risk factors)
- It has been recommended that using rifapentine (as it exists today) be done in situations where there is a high risk of non-adherence or non-completion of treatment, or where other treatment alternatives are not feasible or suitable

Resuming the use of rifapentine (3HP Regimen) to treat LTBI

- Starting and stopping treatment for LTBI is highly discouraged
- Patients need to make informed decisions regarding their health and treatments options that are best suited for them
- For many, the benefits of taking rifapentine are greater than the risk of exposure to the nitrosamine impurity or leaving their latent TB infection untreated
  - especially true for persons at high risk of developing active TB disease (i.e., those with certain medical conditions or on certain immunosuppressant medications) who may find longer or more frequent treatment options too challenging to adhere to
- Other treatment options exist if rifapentine is not right for the client

Resuming the use of rifapentine (3HP Regimen) to treat LTBI

- A patient centered approach to LTBI treatment is an essential component of TB prevention and control and an important step towards TB elimination.
- The best choice for a client with LTBI is a treatment regimen they are comfortable with and most likely to successfully complete
- CHNs should provide the client with the information to help clients understand risks and benefits of each of their treatment choices, including those associated with the nitrosamine impurity currently in rifapentine
- Clients can then make an informed decision whether the 3HP regimen (that includes rifapentine) is the right treatment for them or if they prefer an alternative regimen

The ultimate goal is the successful treatment of LTBI in order to prevent active TB. Helping clients to make an informed choice they are comfortable with means they are more likely to complete treatment successfully.

Thank you!

Questions?