HIV Treatment Monitoring and Antiretroviral Access in SK

Junine Toy, PharmD
Senior Manager, Drug Treatment Program, BC Centre for Excellence in HIV/AIDS

Updated October 2018 by: Saskatchewan Advisory Team
Faculty Disclosures

Junine Toy, PharmD
• None to disclose
Faculty Disclosures

Saskatchewan Advisory Team Disclosure

**Mike Stuber**, BScPharm (Saskatchewan Health Authority)
- Relationships with financial sponsors:
  - **Grants/Research Support:** not applicable
  - **Speakers Bureau/Honoraria:** ViiV, Gilead Sciences
  - **Consulting Fees:** not applicable
  - **Patents:** not applicable

**Yvonne Blonde**, MD (University of Saskatchewan)
- None to disclose

**Kris Stewart**, MD (Saskatchewan Infectious Disease Care Network; Saskatchewan Health Authority; and University of Saskatchewan)
- Relationships with financial sponsors:
  - **Grants/Research Support:** ViiV, Merck, Gilead, AbbVie
  - **Speakers Bureau/Honoraria:** not applicable
  - **Consulting Fees:** not applicable
  - **Patents:** not applicable
Disclosure of Financial Support

• This program has not received any financial or in-kind commercial support

• **Potential for conflicts of interest:**
  • No commercial organization has supported this program.
Mitigating Potential Bias

- The content of the presentation is consistent with guidelines developed by the BC-CfE Committee for Drug Evaluation and Therapy (CDET)
- The content of the presentation has been developed by the speakers
- Generic names of medications are used in place of brand names
In this module, we will discuss how to monitor patients on antiretroviral treatment (ART), including lab monitoring of efficacy and toxicity of treatment, the importance of adherence to ART, monitoring side effects and evaluation for drug interactions.

We will then discuss how to access antiretroviral therapy in Saskatchewan as well as highlight some helpful resources for prescribers.
HIV plasma viral load

- HIV plasma viral load (pVL) is the most important indicator of response to ART.

- Measure pVL at baseline and regularly during therapy
  - Expect 1-2 log decline in pVL by 4 weeks after treatment initiation
  - pVL should be suppressed below level of detection by 3-6 months.

- Frequency of pVL monitoring
  - After initiation of ART, check monthly until <40 copies/mL then every 3-4 months.
  - In clinically stable patients (adherent to ART, pVL <40 copies/mL for 2 years and CD4+ ≥ 350 cells/μL) may extend monitoring to every 6 months.
  - After ART modified check 1 month after switch to confirm effectiveness of regimen.

- Regular clinical and laboratory monitoring is important for HIV patients on ART.
- HIV plasma viral load (pVL) is the most important indicator of response to ART and should be measured at entry into care, at initiation of therapy, and regularly thereafter to confirm adequate response to ART and to confirm adherence.
- Plasma viral load should decline by 1-2 log by 4 weeks after treatment initiation, and suppressed below the limit of quantification by 3-6 months.
- The frequency of pVL monitoring is dependent on stability of the patient and ART regimen.
- After initiation of ART, check pVL monthly until <40 copies/mL then every 3-4 months thereafter.
- In clinically stable patients who are adherent to ART, with pVL consistently <40 c/mL for 2 years and CD4+ count ≥ 350 cells/μL, pVL monitoring may be extended to every six months.
- In virologically suppressed patients in whom ART treatment is modified, pVL should be checked 1 month after the switch to confirm effectiveness of the regimen.
CD4+ count

- **CD4+ response to ART**
  - Immunologic response to ART is variable
  - Adequate CD4+ response usually 50-150 cells/μL increase in the first year

- **Frequency of CD4+ monitoring**
  - **After ART initiation**, monitor in conjunction with pVL or every 3-4 months in the first 2 years
  - **In stable patients** (ART adherent patients with pVL < 40 copies/mL > 2 years and CD4+ ≥ 350 cells/μL) CD4+ monitoring is optional
  - **Change in clinical status** that may result in decreased CD4+, resume CD4+ monitoring
    - Immunosuppressive medications, chemotherapy, interruption of ART
    - pVL rebound while on ART

- CD4+ count is an important marker of immune function and is used to determine the need for opportunistic infection prophylaxis.
- Although immunologic response to ART is variable, an adequate CD4+ response is usually in the range of a 50-150 cells/μL increase in the first year.
- CD4+ count and fraction may be monitored in conjunction with pVL or every 3-4 months in the first 2 years after ART initiation.
- In ART adherent patients with suppressed viral load > 2 years and CD4+ count ≥ 350 cells/μL, CD4+ monitoring is optional as it provides little information to influence clinical management.
- However, CD4+ monitoring should resume if there is a change in clinical status of the patient that may result in decreased CD4+ count (e.g. immunosuppressive medications, chemotherapy, treatment interruption) or if viral load suppression is not maintained while on ART.
Safety labwork

• Safety laboratory parameters to monitor
  • Complete blood count, chemistry profile, liver enzymes, serum creatinine
  • Fasting blood sugar, and serum lipids
  • If on tenofovir DF, urinalysis with urine albumin/creatinine ratio and phosphorus

• Frequency of monitoring
  • Monitor one month after ART initiation or change
  • May coordinate with pVL monitoring
  • Once stable, monitor every 3-6 months
  • More frequent monitoring may be indicated for specific ART or co-medication toxicities, or co-morbid conditions

Safety laboratory parameters (complete blood count, chemistry profile, liver enzymes, serum creatinine, fasting blood sugar and lipids) should be monitored regularly while on treatment.
Additional renal monitoring for individuals on tenofovir DF should include urine for albumin/creatinine ratio, and serum and urine phosphorus.
Safety labwork should be performed one month after initiation or change in antiretroviral therapy, and if stable, every 3-6 months thereafter. Clinicians may wish to coordinate it with pVL monitoring.
More frequent monitoring may be indicated for specific ART or co-medication toxicities (e.g. nevirapine and liver enzymes in first 18 weeks), or if there are co-morbid conditions.
This table summarizes recommended laboratory monitoring for patients receiving ART with frequency of monitoring dependent on stability of the patient. Monitoring may be tailored according to underlying co-morbid conditions, known potential toxicities of specific antiretroviral drugs, and/or concomitant medications.
Patients usually achieve virologic suppression within 3-6 months after ART initiation.

If viral suppression is not achieved, or pVL rebounds to >250 copies/mL, evaluate the patient for treatment failure.

Review potential reasons for inadequate response to treatment (e.g. missed doses, partial regimens, non-adherence to regimen food requirements, drug interactions).

If pVL >250 copies/mL, order HIV resistance test if indicated.

In the setting of virologic failure, resistance testing should be performed on sample(s) drawn when the patient was receiving ART or within 4 weeks of ART discontinuation; however continuation of a failing regimen is not recommended, particularly if the regimen has a low genetic barrier to the development of resistance and is at risk of accumulating resistance mutations and limiting future treatment options.

Results of resistance testing will guide the selection of active antiretrovirals for subsequent regimens.

Consult an HIV expert to evaluate treatment failure and treatment modification.

Isolated low-level detectable pVL<250 copies/mL (“pVL blips”) are not believed to predict treatment failure.
The requisition form for HIV specific laboratory tests can be found on the BC-CfE website. These tests include:

- **Resistance testing** to guide selection of ART.
  - Saskatchewan’s resistance testing is conducted by the BC-CfE.

- **Viral tropism test** prior to initiation of CCR5 antagonist maraviroc.

- **HLA-B*5701 screening** to identify those at risk for abacavir hypersensitivity.

To perform the resistance testing:

- **Resistance test** for mutations in HIV viral reverse transcriptase, protease and integrase genes. This test requires a stored sample of a detectable HIV plasma viral load.

- **CCR5 co-receptor tropism testing** prior to initiating the entry inhibitor maraviroc. This test can be performed on a recent stored plasma sample if pVL > 500 copies/mL or a new whole blood sample if pVL ≤ 500 copies/mL.

- **HLA-B*5701 allele screening** to identify individuals at risk of hypersensitivity to abacavir. This test requires a new blood sample.
• Monitoring beyond lab work is important to ensure ART success.
• At each patient visit, it is important to review adherence to the ARV regimen.
• Monitoring treatment tolerability and providing support and advice for side effect management is also critical.
• An evaluation of drug interactions should be incorporated into routine monitoring.

Other clinical monitoring

• At each patient visit, review the following:

  • **Adherence** to antiretroviral regimen

  • **Treatment tolerability**
    • Inquire about side effects and provide advice for management

  • **Drug interactions**
    • Review all co-medications and supplements for potential interactions.


Adherence

• Strict adherence to ART is key to treatment success
  • Virologic suppression, lower rates of resistance, improved quality of life, improved survival, and decreased risk of HIV transmission.
  • In reality this is not always achieved.
    • Decisions on whether to stop a regimen because of non-adherence are complicated and are made on a case by case basis.

• Assess adherence at each patient visit.
  • Correct meds, doses, timing, food requirements
  • Assess type, pattern and reasons for non-adherence

• Methods
  • Pharmacy records
  • Patient self-report
  • Visual analogue scale
  • Surrogate markers

• Optimal adherence (all medications and doses at time intervals prescribed) is important for various clinical outcomes: maintenance of virologic suppression, decreased rates of development of resistance, improved patient quality of life, improved survival rates and decreased risk of HIV transmission.
• There are challenges with adherence to ART: treatment is lifelong, medication adherence declines over time and can be impacted by factors such as depression, substance use. In addition, successive ART regimens may increase in complexity.
• Due to the importance of adherence, patients should be interviewed regarding medication adherence in a nonjudgmental manner at each visit.
• Assess whether all of the correct medications are taken at the correct dose and timing and with the appropriate food requirements.
• Identify the type, pattern, and reasons for non-adherence so that corrective measures can be taken.
• There are various ways to assess adherence, although there are limitations to each method. A combination of methods such as assessing pharmacy refill records, eliciting patient self report, and verifying surrogate markers such as viral load suppression may be employed.
Improving Adherence

- Simplify regimen, dosing, and food requirements.
- Anticipate and treat side effects
- Address barriers to adherence early
- Use positive reinforcement, engage family, friends and the healthcare team.
- Assess adherence at each clinic visit.
- Systematically monitor treatment efficacy and retention in care
- Anticipate treatment interruptions (e.g. elective surgery)
- Consider ART regimen with lower risk of developing resistance

Strategies to improve adherence may include the following.
- Simplify ART regimen, dosing frequency or pill burden, and prescribe a regimen without food restrictions or requirements if possible.
- Anticipate and manage side effects, especially early in treatment.
- Address psychosocial barriers to adherence including homelessness, lack of transportation, depression, anxiety, active substance or alcohol misuse.
- Linking pill-taking behaviors to other daily activities (e.g. brushing teeth, breakfast, methadone maintenance therapy).
- Use educational aids including pictures, pillboxes, calendars and timers.
- Engage family, friends and a team approach with nurses, pharmacists, peer counselors, etc.
- Assess adherence at every clinic visit in a systematic manner.
- Treatment interruptions are discouraged; however, patients are encouraged to inform care provider if a problem with adherence is anticipated (e.g. elective surgery, prolonged intercurrent illness) so that a plan can be implemented. Expert advice should be obtained.
- Consider prescribing ART regimens that have a lower risk of developing resistance with poor adherence (i.e. boosted protease inhibitor based regimens vs. NNRTI or unboosted PI regimens).
The risk of certain adverse effects may be higher in certain groups.

- For example, nevirapine should not be initiated in women with CD4+ >250 cells/μL, or in men with CD4+ >400 cells/μL due to an increased risk of hepatotoxicity.
- Patients with hepatitis B or C co-infection may be at higher risk of experiencing liver enzyme elevation, and individuals on interacting medications may experience toxicity from ART or the co-medication.
- Important to consider possible AEs when selecting ARVs for the individual patient and monitoring the patient.
The table shows examples of side effects that are specific to certain ARV agents. Some side effects may occur early in treatment (e.g. hypersensitivity, nausea) or later (e.g. decreased bone density). Severe side effects (e.g. hypersensitivity) should be addressed immediately. When possible, switch the likely offending agent to an effective alternative with a different side effect profile. Other side effects may be mild and self-limiting (e.g. nausea, diarrhea) and may be managed with supportive care or non-prescription medications if required.

Examples of adverse effects of specific ARVs

- Abacavir: nausea, headache, hypersensitivity
- Atazanavir + ritonavir: nephrolithiasis, benign hyperbilirubinemia, nausea, diarrhea
- Darunavir/cobicistat: nausea, diarrhea, dyslipidemia
- Dolutegravir: insomnia, nausea
- Efavirenz: neuropsychiatric side effects, rash, dyslipidemia
- Elvitegravir/cobicistat: nausea
- Tenofovir DF: renal dysfunction, decreased bone density

*List not all-inclusive*
Drug interactions

- Common with ARV therapy
- Mechanisms
  - Altered drug absorption (gastric pH, chelation)
  - Altered drug metabolism by enzymes (liver, gut)
  - Effects on membrane transporters
- Potential negative consequences
  - Drug toxicity and non-adherence
  - Viral breakthrough and possible resistance
  - Suboptimal disease management
- Risk factors
  - Protease inhibitors, cobicistat, NNRTIs, HCV, number of co-medications, illicit drug use

### Examples of drug interactions

<table>
<thead>
<tr>
<th>Co-medications</th>
<th>ARVs</th>
<th>Drug Interaction effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton pump inhibitors</td>
<td>Atazanavir, Rilpivirine</td>
<td>Decreased absorption of ARV.</td>
</tr>
<tr>
<td>Polyvalent cations (Mg, Fe, Ca, Al)</td>
<td>Integrase inhibitors</td>
<td>Decreased absorption of integrase inhibitor.</td>
</tr>
<tr>
<td>Methadone</td>
<td>Efavirenz, Nevirapine</td>
<td>Decreased level of methadone.</td>
</tr>
<tr>
<td>Anticonvulsants (phenytoin, carbamazepine, phenobarbital)</td>
<td>Many ARVs</td>
<td>Decreased level of ARV</td>
</tr>
<tr>
<td>Statins</td>
<td>Ritonavir, cobicistat</td>
<td>Increased level of statins.</td>
</tr>
<tr>
<td>Inhaled, nasal, and injectable corticosteroids</td>
<td>Ritonavir, cobicistat</td>
<td>Increased level of corticosteroid.</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors (sildenafil, tadalaful, vardenaful)</td>
<td>Ritonavir, cobicistat</td>
<td>Increased level of phosphodiesterase inhibitor.</td>
</tr>
<tr>
<td>Anticoagulants (warfarin, rivaroxaban)</td>
<td>Protease inhibitors, cobicistat, NNRTIs</td>
<td>Altered level of anticoagulant.</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Many ARVs</td>
<td>Altered level of contraceptive.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Many ARVs</td>
<td>Decreased level of ARV</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Tenofovir</td>
<td>Potential additive nephrotoxicity</td>
</tr>
</tbody>
</table>

- This table lists some important drug interactions with ARVs and co-medications (list not all-inclusive).
- Medications that reduce stomach acid, such as antacids, H2 antagonists and proton pump inhibitors, decrease the absorption of atazanavir and rilpivirine.
- Products containing magnesium, iron and calcium can lower the absorption of integrase inhibitors.
- Older anti-convulsant medications such as phenytoin and carbamazepine will decrease the level of many ARVs.
- “Boosters” such as ritonavir and cobicistat can increase systemic levels of inhaled, nasal, injectable and topical corticosteroids used for asthma, allergic rhinitis, and arthritis and result in Cushingoid symptoms and adrenal suppression.
- Levels of blood thinning products such as warfarin and rivaroxaban can be affected by some antiretrovirals.
- The level and effectiveness of oral contraceptives may be affected by many antiretroviral medications.
Drug interactions should be systematically assessed for at each visit.

- Review and update the patient’s list of medications, including prescription, non-prescription, vitamins, other supplements, and recreational drugs. Also consider inhaled, nasal and topical agents. Document dose, frequency and indication.
- Check for interactions before prescribing.
- Utilize reliable drug interaction resource(s).

Management:
- Assess clinical significance of interaction.
- Dosage adjustment, medication change, spacing of medication timing, or careful monitoring may be required.
- Make a monitoring plan.

Educate the client to check with their physician or pharmacist before starting any new medication or supplement.
Drug Interaction Resources

- Toronto General Hospital Immunodeficiency Clinic HIV/HCV drug therapy guide
- app.hivclinic.ca
- University of Liverpool HIV drug interaction website
- www.hiv-druginteractions.org
- Contact the LINK HIV physician on call through ACAL to for advice
  - 306-655-8008

- Listed above are well-referenced and practical HIV specific drug interaction resources.
The BC Centre for Excellence in HIV/AIDS website provides helpful resources and guidance in obtaining antiretroviral therapy from the program (www.cfenet.ubc.ca)

Resources that can be found on the website include:
- Therapeutic guidelines for antiretroviral treatment in adults
- Guidelines for treatment and prophylaxis of opportunistic infections
- Primary Care Guidelines for HIV positive patients
- Guidelines for HIV Pre-Exposure Prophylaxis (PrEP)
- Guidelines for HIV Post-Exposure Prophylaxis (PEP)
- ARV drug information sheets for the patient
- BC CFE laboratory requisition forms
ARV Drug Coverage

• There is no cost for individuals covered by Non-Insured Health Benefits (NIHB).

• Effective April 2018, the Saskatchewan Ministry of Health announced HIV medications will be provided at no cost for eligible Saskatchewan Health beneficiaries.

  • Includes Pre-Exposure Prophylaxis (PrEP).

  • Eliminates cost-sharing deductibles/co-payments that were previously included as part of the province’s coverage of HIV medications.
Becoming listed as an ARV prescriber in SK

- The Saskatchewan Prescription Drug Plan maintains a list of approved ARV and HCV treatment prescribers (in addition to specialists).

- Individuals with experience in treating HIV and HCV or working in partnership with a specialist may be listed.

- Physicians not on the list may renew Rx’s written by an approved prescriber but once annually an approved physician must renew the Rx.
  - This is in an effort to ensure that appropriate monitoring is occurring
    - CD4, HIV viral load, targeted investigations for treatment related effects
Prescribing Assistance

- Monday to Friday 9am to 5 pm there is a physician on call through the ACAL LINK service for non critical advice.
  - 306-655-8008

- Saskatchewan Disease Care Network (SIDCN) provides e-mail support Monday to Friday 8am-4pm. Replies will be provided by HIV specialists and/or pharmacists.
  - Send questions via the program coordinator: amanda.galambos@sidcn.ca
Summary

- Monitor ART efficacy and toxicity with regular laboratory and clinical monitoring
- Treatment adherence and drug interactions are important to assess at each patient visit
- Seek expert advice for patient management
Contact information:

Amanda Galambos
Saskatchewan Infectious Disease Care Network (SIDCN)
Program Coordinator
amanda.galambos@sidcn.ca