Antiretroviral Therapy Overview

Junine Toy, Pharm D

Clinical Pharmacist
St. Paul's Hospital, Providence Health Care

Jtoy@providencehealth.bc.ca

Objectives

By the end of the unit, you will understand

- Goals of HIV treatment
- Considerations when selecting and initiating antiretroviral therapy
- Recommended initial treatment options
- Monitoring considerations

Treatment

- Since the advent of HIV treatment in Canada, the death rate from AIDS has declined by 94%.
- With appropriate treatment HIV infection has been transformed into a chronic manageable disease.
- Goals of treatment are reduction in HIV-related morbidity, prolonged survival and quality of life, to restore and preserve immunologic function, and to maximally and durably suppress HIV viral load to undetectable levels.
- Treatment of HIV-infected persons is also recommended to prevent the transmission of HIV.
- Treatment is lifelong and does not offer a cure.

Treatment

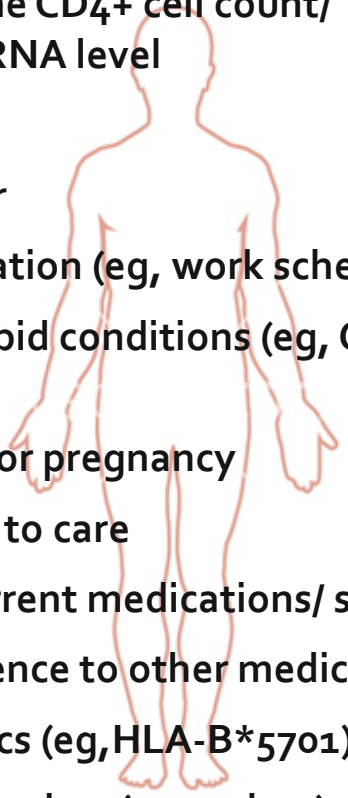
- Antiretroviral therapy (ART) ideally consists of 3 active drugs.
- Many newer treatments have fewer pills and improved tolerability. There are a number of fixed-dose combination tablet options that can be taken once a day.
- High levels of adherence to ART (≥95%) are essential for treatment success and to prevent the development of resistance. Resistance may reduce future treatment options.

Treatment

- In cases of viral resistance, there are better 2nd-line treatment options. Despite improvements, treatment side effects such as renal and bone health remain an issue and the effects of using ART over many decades are not fully known.
- The HIV-positive population is aging. There are more age-related medical conditions to consider. Aging HIV patients are taking more medications, which raises concerns about drug interactions.

Considerations when Selecting Therapy

In general, a simple, well-tolerated and effective regimen is the goal of selecting HIV treatment. There are numerous patient and treatment considerations when selecting first-line regimen as listed below.



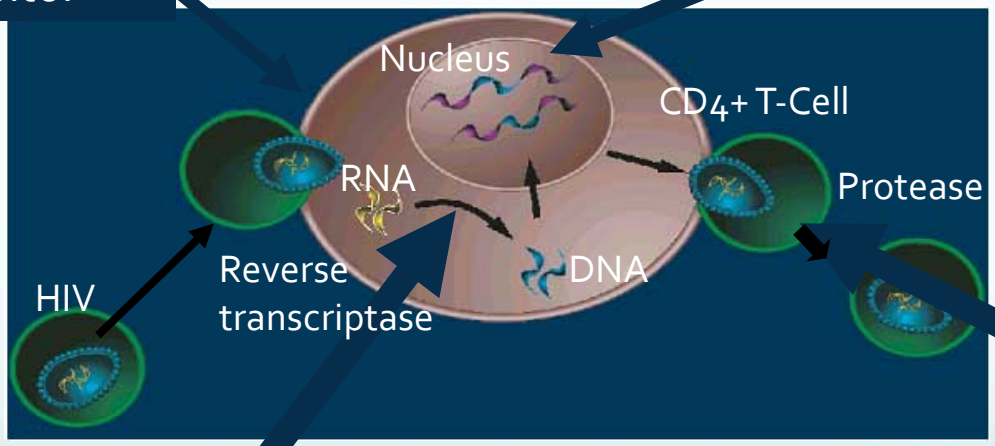
- Baseline CD_4+ cell count/ HIV-1 RNA level
- Age
- Gender
- Occupation (eg, work schedule)
- Comorbid conditions (eg, CV risk, renal, HBV)
- Plans for pregnancy
- Access to care
- Concurrent medications/ supplements
- Adherence to other medications
- Genetics (eg,HLA-B*5701)
- Viral tropism (maraviroc)

Antiretroviral Drug Factors

- Efficacy
- Baseline drug resistance
- Tolerability
- Long-term toxicity/ metabolic effects
- Drug–drug interactions
- Dosing frequency
- Pill burden
- Food requirement
- Pharmacokinetics
- Consequences of failure (resistance)
- Cost

Targets of HIV Medications

All available antiretroviral (ARV) medications work by targeting the HIV life cycle. HIV (shown in green) enters the human CD_4 cell and replicates in a multi-step process that involves a number of enzymes.



- Entry inhibitor (CCR5 antagonist)
- Fusion Inhibitor

- Integrase Inhibitors

Reverse transcriptase inhibitors (RTI)
- Nucleoside/tide analogue (N(t)RTI)
- Non-nucleoside analogue (NNRTI)

- Protease inhibitors (PI)

Available Antiretroviral Agents

There are currently 6 antiretroviral (ARV) drug classes and 26 ARV medications available in Canada. They are named below followed their common abbreviation.

Nucleoside/tide analogue RTI (NRTI)

- Abacavir (ABC)
- Didanosine (DDI)
- Emtricitabine (FTC) in Truvada®
- Lamivudine (3TC)
- Stavudine (d_4T)
- Tenofovir (TDF)
- Zidovudine (AZT, ZDV)

Non-nucleoside analogue RTI (NNRTI)

- Efavirenz (EFV)
- Etravirine (ETV)
- Nevirapine (NVP)
- Rilpivirine (RPV)
- Delavirdine (DLV)

Entry Inhibitor (CCR_5 Inhibitor)

- Maraviroc (MVC)

Protease inhibitor (PI)

- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (fos-APV)
- Indinavir (IDV)
- Lopinavir (LPV) in Kaletra®
- Nelfinavir (NLF)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV)

Integrase Inhibitor

- Raltegravir (RAL)
- Elvitegravir (EVG) in Stribild®
- Dolutegravir (DTG)

Fusion Inhibitor

- Enfuvirtide (T20)

Laboratory Testing

- Laboratory tests are used to aid in the selection of ART and for monitoring safety and effectiveness.
- CD_4 count and plasma HIV viral load are used to assess immune function and level of HIV viremia respectively.
- HIV resistance testing should be performed at entry into care, and if treatment is deferred, repeated prior to ART initiation.
- Special blood tests include HLA-B*5701 screening to identify those at risk of abacavir hypersensitivity and CCR5 co-receptor tropism testing prior to initiating maraviroc.
- Other tests include complete blood count, chemistry profile, liver enzymes, kidney function, hepatitis A, B, and C, fasting blood sugar, and serum lipids.

Treatment Options: Initial Therapy

- Recommended initial treatment consists of a 2 drug nucleoside/nucleotide analogue backbone PLUS a 3rd active agent from one of the following classes: an NNRTI, a ritonavir-boosted protease inhibitor or an integrase inhibitor.
- In BC, the NNRTI efavirenz or ritonavir-boosted atazanavir are preferred initial choices for 3rd drug due to clinical experience and sequencing considerations.
- However, based on the clinical circumstance (e.g. co-morbidities, drug interactions, risk of non-adherence or pre-existing viral resistance) an alternative 3rd agent may be chosen.
- Examples of alternative agents include rilpivirine, ritonavir-boosted darunavir, dolutegravir, or raltegravir.

Initial Therapy: Dual-NRTI Pairs

- **tenofovir/emtricitabine (Truvada®):** a recommended NRTI backbone
  - Dosage: One pill once daily
  - Use: Demonstrated effectiveness in all viral load and CD_4 strata, and both components are active against hepatitis B.
  - Adverse Effects: Tenofovir has the potential for renal side effects and decreased bone mineral density.
- **abacavir/lamivudine (Kivexa®):** a recommended NRTI backbone
  - Dosage: One pill once daily
  - Use: May be less effective if baseline viral load is >100,000 copies/mL, particularly with efavirenz and boosted atazanavir.
  - Adverse Effects: There is a risk of severe abacavir allergy in individuals testing positive for the HLA-B*5701 allele (approx. 5%) and a possible association with abacavir and cardiovascular events; therefore caution should be exercised in high cardiovascular risk individuals.
- **zidovudine/lamivudine (Combivir®):** an alternative NRTI backbone
  - Dosage: Twice daily
  - Use: Used in pregnancy due to known safety to the fetus.
  - Adverse Effects: Nausea, headache, anemia.

Initial Regimens

The following regimens may be used regardless of baseline viral load or CD_4 count.

NNRTI-based	* Efavirenz/tenofovir/emtricitabine (Atripla®)[1] daily
PI-based	* Atazanavir/ritonavir[2] + tenofovir/emtricitabine (Truvada®) daily • Darunavir/ritonavir + tenofovir/emtricitabine (Truvada®) daily
INSTI-based	• Dolutegravir + abacavir/lamivudine (Kivexa®)[3] daily • Dolutegravir + tenofovir/emtricitabine (Truvada®) daily • Elvitegravir/cobicistat/tenofovir/emtricitabine (Stribild®)[4] daily • Raltegravir twice daily + tenofovir/emtricitabine (Truvada®) daily

Notes:

* This is a preferred initial regimen in the BC-CfE Therapeutic Guidelines

Lamivudine can be used in place of emtricitabine and vice versa; tenofovir: caution if renal insufficiency

1. Consider alternative to efavirenz in women who plan to become pregnant or are not using effective contraception.
2. Atazanavir/ritonavir should not be used in patients who take high dose proton pump inhibitors..
3. Abacavir should be used only if HLA-B*5701 is negative; caution if high risk of cardiovascular disease.
4. Elvitegravir/cobicistat/tenofovir/emtricitabine (Stribild) should be started only if creatinine clearance >70 mL/min.

Initial Regimens

Based on clinical trials, the regimens below are recommended only if pre-treatment HIV viral load is <100,000 copies/mL.

NNRTI-based	• Efavirenz + abacavir/lamivudine (Kivexa®)[1,2] daily • Rilpivirine/tenofovir/emtricitabine (Complera®) daily
PI-based	• atazanavir/ritonavir[3] + abacavir/lamivudine (Kivexa®)[2] daily

Notes:

Lamivudine can be used in place of emtricitabine and vice versa; tenofovir: caution if renal insufficiency

1. Consider alternative to efavirenz in women who plan to become pregnant or are not using effective contraception.
2. Abacavir should be used only if HLA-B*5701 is negative; caution if high risk of cardiovascular disease.
3. Atazanavir/ritonavir should not be used in patients who take high dose proton pump inhibitors.

Individualizing First-line Therapy

Treatment should be individualized to the specific circumstances. Below are some examples.

Circumstance	Agents
No genotype	∗Use boosted protease inhibitor
High HIV-1 RNA	∗Caution with abacavir, rilpivirine
Renal disease	∗Caution with tenofovir, atazanavir/ritonavir
Dyslipidemia	∗raltegravir, dolutegravir, rilpivirine, nevirapine most lipid neutral
CV risk factors	∗Possible association with abacavir, didanosine, lopinavir/ritonavir ∗No data for darunavir/ritonavir, integrase inhibitors, maraviroc
Pregnancy	∗Preferred: zidovudine/lamivudine + nevirapine, lopinavir/ritonavir, or atazanavir/ritonavir ∗Avoid efavirenz, but may be used after first 5-6 wks
Chronic HBV infection	∗Preferred tenofovir + lamivudine or emtricitabine
Decreased bone mineral density	∗Caution with tenofovir
Concerns about CNS effects	∗Caution with efavirenz for at least first month

Readiness for Therapy: A Key Decision Point

- Protease inhibitor (PI) based therapy has a lower risk of resistance at treatment failure vs. NNRTI- and raltegravir-based strategies.
- Adherence is more likely with a simple regimen such as one pill once a day.
- Complicated regimens with frequent dosing, food requirements and those with more adverse effects may affect adherence.
- Regimens with higher risk of resistance at failure should also be avoided.

Adverse Effects

- Modern ART is associated with fewer side effects than its predecessors (e.g. less gastrointestinal effects, lipodystrophy, neuropathy). However, ART may still be associated with short- and long-term side effects that range from mild and self-limited to persistent or severe. It is important to counsel patients to seek advice if side effects occur, and to recognize severe side effects.
- Gastrointestinal disturbances such as nausea, diarrhea, bloating and flatulence may occur when initiating treatment, especially with protease inhibitors. These usually improve or resolve with time.

Adverse Effects

- Other potential side effects depend on the agent, including dyslipidemia (e.g. protease inhibitors), hepatotoxicity (e.g. nevirapine), rash (NNRTIs), neuropsychiatric side effects (e.g. efavirenz), benign hyperbilirubinemia (e.g. atazanavir), renal dysfunction (e.g. tenofovir), severe allergy (e.g. abacavir).
- Depending on the circumstance, management may include supportive or pharmacologic treatment or switching agents.

ARV Administration: Food and Timing

- Patients should incorporate their ART dosing into their daily routine, and take them at the same time(s) every day to maintain consistent medication levels.
- Food intake is an important consideration for ART and can often improve tolerability with treatment initiation.
- Food intake is also essential for maximal absorption and effect of a number of antiretrovirals. These include atazanavir, darunavir, saquinavir, ritonavir, etravirine, elvitegravir/cobicistat/tenofovir/emtricitabine (Stribild®), and rilpivirine..
- Patients should be counseled on how to handle missed doses (i.e., better late than never) and to never take partial regimens, make their own dose adjustments or stop their regimen without the advice of their healthcare provider.

Drug Interactions

- Drug interactions with ART are common, and may involve prescription drugs, over-the-counter drugs, vitamins, herbal or complementary therapies, street drugs, puffers, or nasal sprays
- A drug interaction may lead to increased side effects or decreased effectiveness of the ARV or its co-medications. Management may involve separate dose timing, dose adjustment, or changing therapy.
- A pharmacist should be consulted before initiating any new medication or supplement. In BC, call 1-888-511-6222.

Drug Interactions

- The following are some important examples of ART drug interactions:
  - Antacids and proton pump inhibitors decrease dissolution and absorption of atazanavir and rilpivirine.
  - Antacids form insoluble complexes with integrase inhibitors in the gut resulting in decreased integrase inhibitor levels.
  - Ritonavir increases side effects from steroid puffers (e.g. Fluticasone) by blocking the liver from processing of the steroid and increasing steroid levels.
  - Efavirenz and nevirapine may lead to opioid withdrawal by increasing the processing of methadone by the liver.

Treatment Monitoring Summary

- It is important to monitor patients for safety and effectiveness.
- Monitor response to ART with HIV plasma viral load (pVL) 4 weeks after start, then every 4-8 weeks until suppressed to <40 copies/mL (expected within 3-6 months).
- Extend pVL testing to every 3-4 months for stable patients and consider every 6months for stable, adherent patients with pVL suppressed greater than 2 years.
- Isolated pVL "blips" (transient low-level detectable HIV pVL <200 copies/mL) are not believed to predict treatment failure.

Treatment Monitoring Summary

- CD_4 count is checked every 3-6 months after ART initiation. This can be extended to annually if patient is clinically stable and CD_4>300 cells/uL, or is optional if CD_4>500 cells/uL.
- For safety, monitor complete blood count + differential, liver enzymes, serum creatinine, urinalysis with urine albumin/creatinine ratio and phosphorus if on tenofovir.
- Monitor patients for side effects and treatment adherence, and review co-medications / supplements at each visit.

Management of Virologic Failure

- Patients who do not achieve undetectable plasma viral load (pVL) or experience viral load rebound to >200 copies/mL are at risk of developing ARV resistance mutations.
- Repeat pVL viral load should be performed and expert consultation is recommended for management.
- Clinicians should review potential causes of failure including non-adherence, side effects, food intake, malabsorption, drug interactions and address any modifiable causes.

Management of Virologic Failure

- Order resistance test if HIV pVL>200 copies/mL while the patient is still taking a failing regimen or within 4 weeks of discontinuation.
- If greater than 4 weeks since ART discontinuation, resistance testing may not detect previously selected mutations. Results should be interpreted with history of ART, adherence to ART, and prior and current ARV resistance test results.
- Ideally, a new ARV regimen should contain 3 fully active drugs.

Summary

- HIV treatment should be offered to patients who are ready to start.
- Safety and tolerability of ARV treatment has improved and many simple treatment options are now available.
- Consider the whole patient when selecting the ARV regimen. Adherence, baseline viral load, drug resistance, and co-morbidities are important considerations.
- There are significant drug interactions with multiple mechanisms.