ESTIMATED PREVALENCE OF HIV INFECTION:

- Number of persons living with HIV (PLWH) at end of 2014
- Worldwide: ~ 37 million, Canada: 54,000 – 76,000
- BC: 12,100 (range 9,700 – 14,500)
  - MSM (men who have sex with men): 49%
  - PWID (person who inject drugs): 28%
  - Heterosexual: 22%
  - Other (blood product, perinatal, occupational): 1%
- HIV diagnoses in BC and Canada decline over time

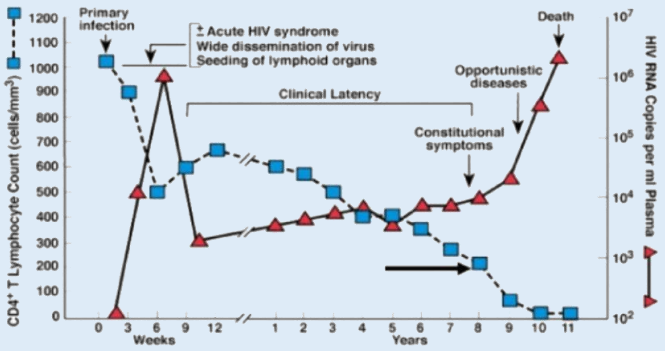
HIV TRANSMISSION:

- Unprotected sexual intercourse with an infected partner
- Vertical transmission (from mother to child)
  - In utero, during delivery, breast milk
- Injection drug use
  - Rare: infected blood/blood products

HIV TESTING GUIDELINES:

- **Routinely** (every 5 years) to all patients aged 18-70 years
  - **Every year** to all patients aged 18-70 years who belong to populations with a higher burden of HIV infection
- **Once** for patients > 70 years of age, if HIV status is not known
- **All patients** when:
  - Ordering dx bloodwork for a new or worsening medical condition
  - They present with sx of HIV infection or advanced HIV disease
  - They or their providers identify a risk for HIV acquisition
  - They request an IV test
  - They are pregnant
  - You test for or diagnose an STI, hep C, hep B or TB

NATURAL HISTORY OF HIV INFECTION:



- Red triangle = HIV viral load = amount of virus in blood volume
- Blue square = CD4 counts = measure of immune system
- HIV viral load and CD4 counts have an inverse relationship

GOALS OF HIV TREATMENT:

- Maximally and durably suppress HIV RNA (viral load)
  - Reduce transmission and population benefit
- Restore and preserve immune function
- Reduce HIV-related morbidity
- Prolong duration and quality of survival
- Prevent HIV transmission

WHEN TO START ANTIRETROVIRAL THERAPY:

- Balance in favour of earlier initiation, due to evidence that supports the importance of preserving immunity, decreasing inflammation and prevention of HIV transmission

BEFORE	• Drug toxicity • Preservation of limited treatment options • Cost
NOW	• Effects of uncontrolled viremia at all CD4+ levels • Increased txt options: improved potency, tolerability, durability, simplicity • Increased ability to suppress multidrug resistance virus and decrease emergence of resistance • Prevents HIV transmission

EVIDENCE FOR EARLY ART INITIATION:

- Untreated HIV associated with development of AIDS and non-AIDS defining conditions
  - Early ART treatment = significant reduction
  - Early ART may prevent end-organ damage while deferred ART may not repair damage acquired earlier
- Potential decrease in risk of complications:
  - HIV associated nephropathy
  - Liver disease progression from hep B or C
  - Cardiovascular disease
  - Malignancies (AIDS defining and non-AIDS defining)
  - Neurocognitive decline
  - Blunted immunological response owing to ART initiation at older age
  - Persistent T-cell activation and inflammation

RECOMMENDATIONS FOR STARTING ART:

- Antiretroviral therapy (ART) is strongly recommended for **all** persons living with HIV to reduce the risk of disease progression, regardless of CD4+ count or stage of disease
  - Also recommended to diminish risk of HIV transmission
- Persons starting ART should be willing and able to commit to lifelong txt and understand the benefits and risks of therapy and importance of adherence
- Early initiation → better immunologic response & clinical outcomes
- Therapy may be postponed on a case-by-case basis, based on clinical or psychosocial factors

TARGETS OF HIV MEDICATION:

ENTRY INHIBITORS	CC45 antagonist	• Enfuvirtide
	Fusion inhibitor	• Maraviroc
REVERSE TRANSCRIPTASE INHIBITORS	Nucleotide analogue reverse transcriptase inhibitor (NRTI)	• Abacavir • Didanoside • Emtricitabine • Lamivudine • Stavudine • Tenofovir DF • Tenofovir alafenamide • Zidovudine
	Non-nucleoside reverse transcriptase inhibitor (NNRTI)	• Efavirenz • Etravirine • Nevirapine • Rilpivirine • Delavirdine
INTEGRASE INHIBITORS (II, INSTI)	• Dolutegravir • Elvitegravir • Raltegravir	
PROTEASE INHIBITORS (PI)	• Atazanavir • Daraunavir • Fosamprenavir • Indinavir • Tipranavir	• Lopinavir/ritononavir • Nelfinavir • Ritonavir • Saquinavir

PHARMACOKINETIC ENHANCERS: ritonavir and cobicistat

- Agents used as pharmacokinetic "boosters"
- Potent inhibition of CYP3A4 in gut and liver to enhance drug exposure

RITONAVIR	• Non-selective CYP enzyme inhibition • Metabolic and GI side effects • Low dose used to boost other protease inhibitors
COBICSTAT	• More selective enzyme inhibition (CYP3A, CYP2D6) • No anti-HIV effect • GI side effects, benign ↑ creatinine • Easier to co-formulate with other drugs (into one pill)

INITIAL THERAPY: TRIPLE THERAPY – should be individualzed

2 NRTI BACKBONE	PLUS ONE OF THE FOLLOWING
Tenefovir DF-emtricitabine (Truvada) Abacavir-lamivudine (Kivexa)	**PROTEASE INHIBITOR W/ BOOSTER** - atazanavir + ritonavir - darunavir – cobicistat
	NNRTI
	INTEGRASE INHIBITOR

Fusion inhibitor or CCR5 antagonist regimens NOT recommended for initial txt

SELECTING INITIAL ART REGIMEN: FACTORS TO CONSIDER

PATIENT AND VIRAL CHARACTERISTICS	• HIV RNA; CD4 count • HIV drug resistance test results • HLA-B*5701 (abacavir hypersensitivity) • Patient preference • Anticipated adherence
CO-MORBIDITIES	• CVD, hyperlipidemia, renal disease, osteoporosis, psychiatric illness, others • Pregnancy or pregnancy potential • Co-infections: hep B, hep C, TB
REGIMEN CHARACTERISTICS	• Genetic barrier to resistance • Potential adverse effects • Drug interactions with other medications • Convenience (pill #, dosing frequency, fixed-dose combinations, food requirements) • Cost

BASELINE LAB EVALUATION:

- HIV antigen/antibody test
- HIV RNA (viral load)
- HIV drug resistance (genotype)
- CD4 (T-lymphocyte) cell count
- HLA-B*5701 status
- CBC, TAA, BUN, Cr
- Urinalysis
- Chemistry profile
- Hep A, B, C serologies
- FBG, serum lipids

HLA-B*5701 SCREENING FOR ABACAVIR HYPERSENSITIVITY:

- Potentially life-threatening hypersensitivity reaction associated with HLA-B*570 allele
  - One-time screening required prior to prescribing abacavir
  - Abacavir contraindicated if HLA-B*5701 positive (5% prevalence)
- Median reaction onset = 9 days (90% within 6 weeks)
  - Fever, malaise, myalgia, arthralgia
  - Diarrhea, vomiting, abdominal pain
  - Dyspnea, respiratory symptoms
  - Rash
- Patients, regardless of HLA-B*5701 status, should not be re-challenged if hypersensitivity is suspected

INITIAL THERAPY: NRTI BACKBONE OPTIONS

KIVEXA (abacavir/ lamivudine)	• Once daily dosing, with or without food • Avoid if **HLA-B*5701 positive** (risk of hypersensitivity reaction) • Possible inferior efficacy if baseline **HIV RNA > 100,000** copies/mL (with efavirenz or boosted-atazanavir)
TRUVADA (TDF/emtricitabine)	• Once-daily dosing, with or without food • High virologic efficacy • Active against **hepatitis B** • Potential renal toxicity and reduction in BMD
DESCOVY (TAF/emtricitabine)	• BC-CfE restricted use (if unable to use above) • Less renal and bone toxicity than TDF-FTC

INITIAL REGIMENS: regardless of baseline HIV RNA or CD4 count

NNRTI based	• Efavirenz/Truvada (Atripla) • Efavirenz + Kivexa • Rilpivirine/Truvada (Complera)
PI based with booster	• Darunavir/ritonavir or cobistat + Truvada or Kivexa • Darunavir/ritonavir or darunavir/cobistat + Kivexa • Atazanavir/ritonavir + Truvada or Kivexa • Lopinavir/ritonavir + Truvada or Kivexa
Integrase inhibitor based	• Dolutegravir / Kivexa (Triumeq) • Dolutegravir + Truvada • Elvitegravir/cobicstat/Truvada (Stribild) • Raltegravir + Truvada or Kivexa

- **ARVs NOT RECOMMENDED:** delavirdine, didanosine, indinavir, nelfinavir, stavudine
  - Suboptimal potency, excess toxicity, high pull burden or pharmacologic concerns
- **REGIMENS NOT RECOMMENDED:** mono or dual therapy, triple NRTI

INDIVIDUALIZING THERAPY:

	Recommendation	Reason
BASELINE CHARACTERISTICS:		
CD4+ count < 200 cells/Ul	DON'T use rilpivirine	Higher rate of virologic failure
HIV RNA > 100,000 copies/mL	DON'T use rilpivirine	
	CAUTION with Kivexa (with efavirenz or atazanavir-ritonavir)	
HLA-B*5701 positive	DON'T use abacavir	Potentially fatal hypersensitivity reaction
If txt must be started before resistance tests	AVOID NNRTI	NNRTI resistance mutations more likely transmitted
	USE boosted duranavir (or other PI) + Truvada	Resistance to darunavir rare
CO-MORBIDITIES		
HEP B co-infection	USE tenofovir + lamivudine or emtricitabine	These ARVs are active against hepatitis B
CKD (CrCl < 60)	AVOID TDF	TDF associated with proximal renal tubulopathy
	USE abacavir or TAF	• TAF has lesser renal impact than TDF • Abacavir not associated with renal dysfunction
	Some NRTIs may require renal dose adjustment	Many NRTIs are renally eliminated
Osteoporosis	Avoid TDF	TDF associated with reduced BMD
	USE abacavir or TAF	
Psychiatric illness	AVOID efavirenz	Efavirenz or rilpivirine may exacerbate psychiatric symptoms
	CAUTION with rilpivirine	
	MONITOR integrase inhibitors	IIs associated with neuropsychiatric effects
PILL BURDEN AND ADHERENCE		
One pill, once daily regimen	Dolutegravir/abcavir/lamivudine (**Triumeq**)	Consider patient and regimen characteristics (ex// potency, food requirement or restriction, ADRs, DDIs) May not be appropriate for all individuals
	Efavirenz/emtricitabine/TDF (**Atripla**)	
	Elvitegravir/cobicistat/ emtricitabine/TDF (**Stribild**)	
	Rilpivirine/emtricitabine/TDF (**Complera**)	
FOOD EFFECT		
Food required	• Atazanavir • Darunavir • Ritonavir • Etravirine • Rilpivirine • Stribild (combo pill)	
Empty stomach	Efavirenz (food increases absorption and may increase neuropsychiatric effects)	
W/ or W/O food	• Dolutegravir • Raltegravir • Tenofovir • Abacavir • Lamivudine • Emtricitabine	

COMPARISON OF ART REGIMENS:

	ATV,RTV, TDF/FTC	DRV/COBI, TDF/FTC	RAL + TDF/FTC	EFV/ TDF/FTC (Atripla®)	RPV/ TDF/FTC (Complera®)	EVG/COBI/ TDF/FTC (Stribild®)	DTG/ ABC/3TC (Triumeq®)
Daily pill burden	3	2	3	1	1	1	1
Times per day	1	1	1-2	1	1	1	1
Food requirement or restriction							
CNS side effects							
GI side effects							
Drug interactions							
Use in high pVL							

HIV RNA PLASMA VIRAL LOAD (pVL):

- Most important indicator of response to ART
- Expect rapid decline after treatment initiation
  - ↓ 1-2 $\log_{10}$ (copies/mL) by 1 month
  - pVL suppression by 3-6 months (i.e. < 40 copies/mL)
- If pVL not suppressed or "rebounds" to > 250 copies/mL
  - Evaluate treatment adherence, drug interactions, etc
  - Perform HIV resistance test on sample(s) when patient receiving ART or within 4 weeks of ART discontinuation

LABORATORY MONITORING:

	Test	Base-line	First 2 years	After 2 years
HIV RNA	HIV RNA pVL	√	Monthly until < 40, then q3m	Every 6 months
CD4 count	Absolute CD4 count, CD4 fraction	√	Monthly until > 200, then q3m	Once CD4 ≥ 350 monitoring optional
HEME	CBC dif, platelet	√	At 1 month, then q3m	Every 6 months
RENAL	SCr, eGFR, PO4, urinalysis, spot urine for ALB:Cr	√		
LIVER	ALT, AST, total bilirubin, INR	√		
FASTING LIPIDS	Total chol, HDL, LDL, TGs and/or ApoB	√	At 1 month, then q6m	
ENDO	FBG, HbA1C	√		

TREATMENT MONITORING: at each patient visit

- Adherence to ART regimen: missed doses? Food requirements?
- Treatment tolerability: any side effects?
- Drug interactions: new Rx, non-Rx, herbals, or other supplements?

ADHERENCE:

STRICT ADHERENCE IS KEY TO	• Virologic suppression • Lower rates of resistance • Better quality of life • Improved survival • Decreased risk of HIV transmission
ADHERENCE CHALLENGES	• Treatment is lifelong • Medication adherence declines over time • Successive regimens may increase in complexity
ASSESSING ADHERENCE	• Assess adherence at every clinic or pharmacy visit in a non-judgemental manner • Identify type, pattern & reasons for nonadherence
MEASURING ADHERENCE	• Patient report • Pharmacy dispensing records • Surrogate markers (HIV viral load, drug levels)
IMPROVING ADHERENCE	• Educate on HIV disease, treatment & prevention • Establish readiness to start therapy • Individualize treatment, with patient involvement • Simplify regimen, dosing, and food requirements • Anticipate and treat side effects • Identify and address barriers to adherence early • Engage family and friends • Use positive reinforcement • Systematically monitor treatment efficacy and retention in care
CAUTION WHEN ART IS INTERRUPTED	• Stopping ART regimen with imbalance in drug $t_{1/2}$ • Long drug half-life + low genetic barrier to resistance + replicating virus may lead to development of drug resistance • Evaluate BEFORE restarting!

ART-ASSOCIATED ADVERSE EFFECTS:

- Newer ARV regimens are associated with fewer serious and intolerable ADRs
- Long-term complications of ART may be underestimated
- Short and long-term ADRs should be considered when selecting ART
- Consider prior drug intolerance, co-medications and co-morbidities
- Risk of certain ADRs may be higher in certain groups

ADVERSE EFFECTS OF SELECT ARVs:

ARV	POTENTIALLY SEVERE	OTHER
Abacavir	Hypersensitivity (HLA-B*5701 +ve_	
Tenofovir DF	Renal impairment, osteoporosis	Headache, GI discomfort
Efavirenz	Rash, teratogenicity, neuropsychiatric effects (common), QT prolongation	Dyslipidemia
Atazanavir (boosted)	Nephrolithiasis, cholelithiasis, PR interval prolongation, rash	Jaundice, GI intolerance
Darunavir (boosted)	Rash (10%), contains sulfonamide moiety, hepatotoxicity	Dyslipidemia, GI intolerance
Dolutegravir	Depression (rare), hypersensitivity	Insomnia, headache, benign ↑ creatinine
Elvitegravir/ cobicistat	Depression (rare)	Nausea, diarrhea, benign ↑ creatinine

ADVERSE EFFECS OF ARVs:

RASH	NNRTIs	• Most common (especially nevirapine) • Most cases occur within first 6 wks • Usually mild/mod but can be serious (SJS)
	PIs	• Atazanavir • Lopinavir • Daranuvir • Ritonavir • Fosamprenavir • Tipranavir
	IIs	• RARE
	NRTIs	• Abacavir (consider hypersensitivity syndrome) • Emtricitabine may cause hyperpigmentation
	CD45A	• Maraviroc
HEPATO-TOXICITY		• Severity variable: usually asymptomatic, may resolve without treatment interruption
	Any NNRTI	• Nevirapine: risk of severe hepatitis in first few months of use (monitor liver enzymes closely) ○ Increased risk in chronic hep B and C, women, and high CD4 count at initiation (>250 women, > 400 men)
	PIs	• Especially tipranavir or ritonavir • Increased risk in hep B or C, alcohol use, other hepatotoxins
	NRTIs	• Steatosis (zidovudine, stavudine, didanosine)
HEPATIC		• Severe acute exacerbation of hepatitis may occur in pts with HIV/Hep B co-infection who D/C: ○ Tenofovir (DF or AF), lamivudine, emtricitabine • Benign jaundice due to indirect hyperbilirubinemia caused by atazanavir or indinavir
RENAL EFFECTS	RENAL FAILURE	• TDF: ↑ Cr, proteinuria, glycosuria, hypoPO4 ○ Concurrent PI use may increase risk • Monitor SCr, other renal paramters
	NEPHRO-LITHIASIS	• Atazanvir, indinavir • Replace offending ARV + supportive care
	BENIGN ↑ SCr	• Cobicistat, dolutegravir, rilpivirine
BONE DENSITY EFFECTS	TDF	• Associated with greater BMD loss than any other NRTIs (including TAF) • Decreases in BMD seen after initiation of any ART regimen
	Other risks	• Low body weight, female, white or Asian ethnicity, older age, alcohol or tobacco use, hypogonadism, vit D deficiency, CS exposure
	Manage	• Alternative to TDF, calcium + vitamin D, bisphosphonate, weight-bearing exercise

ADVERSE EFFECS OF ARVs (CONTINUED):

DYSLIPID-EMIA	↑ LDL, TG, chol	• Boosted PIs, efavirenz, elvitegravir-cobicistat, TAF, stavudine, zidovudine	
	↑ HDL	• Boosted PIs, efavirenz, elvitegravir-cobicistat, TAF	

	MANAGE	• Monitor regularly
		• Lipid-lowering agent if indicated
		  ○ Caution PIs or cobicistat + certain statins
		• May consider ARV switch
		  ○ Raltegravir, dolutegravir, rilpivirine	

CARDIAC	CVE	• Some cohort studies suggest increased risk of CVE with recent or current use of certain ARVs ○ Abacavir, PIs (darunavir, fosamprenavir, lopinavir, indinavir), didanosine	
	QTc prolong	• Efavirenz, rilpivirine • Saquinavir/ritonavir	
	PR prolong	• Boosted saquinavir, atazanavir, lopinavir	
NEURO-PSYCH	NNRTIs	Efavirenz	• Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation • Sx usually diminish after 2-4 wks • Bedtime & empty stomach administration recommended
		Rilpivirine	• Sleep disturbances, depression
	Integrase Inhibitors	• Insomnia, depression, suicidality	

ART DRUG INTERACTIONS: high potential with ART (27-41% patients)

MAJOR MECHANISMS	• Altered drug absorption (gastric pH, chelation) • Altered drug metabolism (gut, liver) • Effects on membrane transporters	
RISK FACTORS	INHIBITORS	• Protease inhibitors, cobicistat
	INDUCERS	• NNRTIs
	OTHER	• # of co-medications, illicit drug use
ASSESS DRUG INTERACTIONS	• Check for interactions before prescribing • Assess co-medications at each visit (ARVs not on PNET) • Utilize reliable drug interaction resources	
MANAGEMENT	• Assess clinical significance of interaction • Dose adjustment, separation of administration, medication change may be required • Monitoring plan	

EXAMPLES OF DRUG INTERACTIONS:

CO-MEDICATION	ARV	EFFECT
PPIs	Atazanavir, rilpivirine	↓ absorption of ARV
Polyvalent cations (Mg, Fe, Ca, Al)	Integrase inhibitors	↓ absorption of II
Anticonvulsants (phenytoin, CBZ, phenobarbital)	Many ARVs	↓ level of ARV
Rifampin		
Statins	Ritonavir, cobistat	↑ co-medication
Inhaled corticosteroids **		
PDE5 inhibitors		
Anticoagulants (warfarin, rivaroxaban)	Protease inhibitors, cobicistat, NNRTIs	Altered level of anticoagulant
Oral contraceptives	Many ARVs	Altered level of OC
Methadone	Efavirenz, nevirapine	↓ level methadone
NSAIDs	TDF	Potential additive nephrotoxicity

** ritonavir inhibits metabolism of many corticosteroids (CYP3A4)

- Ritonavir ↑ fluticasone AUC 350-fold = avoid (ritonavir or cobicistat)
- Increased risk of Cushingoid symptoms, adrenal suppression
- Reported with inhaled, intranasal, injectable and topical steroids
  - Alternative to inhaled steroid?
  - Substitute CS with safer profile – beclomethasone, ciclesonide, flunisolide
  - Use lowest effective dose
  - Be vigilant of corticosteroid toxicity (screening AM cortisol)
  - Consider change ARVs to non-ritonavir or cobicistat based regimen

BC-CfE DRUG FORMULARY:

- Antiretrovirals
- Select medications for indicator diseases of AIDs
  - Ex// treatment for mycobacterium avium complex (MAC)

ART PRESCRIPTION REQUEST FORM:

- Any licensed BC physician
- Submit for:
  - New or change in regimen
  - New to BC
  - > 6 months off therapy
- CfE clinician review (approx. 2 business days)

SUMMARY:

- ART is recommended for all patients regardless of CD4 count
- Treatment should be individualized based on viral, patient and drug treatment characteristics
- Adherence is key to virologic suppression + prevention of resistance
- SE and DDI management are important for successful ARV therapy
- In BC, ART is available through the BC CFE in HIV/AIDs Drug Treatment Program and its designated pharmacies