CLINICAL FEATURE

Taking a stab at HIV

The advent of long-acting antiretroviral therapies for HIV suppression and prevention

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Since the late 1990s, standard antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection has consisted of three active agents in order to maintain viral suppression, reduce morbidity and mortality, improve quality of life and minimize transmission.[1] Injectable therapies, such as intravenous zidovudine[2] and subcutaneous enfuvirtide,[3] are occasionally used in specific settings; however, these drugs have largely fallen out of favour due to inconvenience and poor tolerability.[2,3] The recent advent of new long-acting injectable antiretrovirals offers the possibility to simplify or eliminate oral pill burden and decrease dosing frequency, which can improve adherence and reduce stigma. Currently, three long-acting antiretrovirals (ARVs) are approved in Canada: cabotegravir,[4] rilpivirine[4] and lenacapavir.[5] This article reviews the approved and potential roles of these agents in HIV treatment and prevention, with a focus on considerations for community pharmacists.

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CABOTEGRAVIR/RILPIVIRINE (CABENUVA)

This regimen consists of the new integrase strand transfer inhibitor (INSTI), cabotegravir, and the previously approved non-nucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine. It is a complete regimen for treatment of HIV-1 in individuals 12 years of age or older who are currently virologically suppressed on oral therapy with no resistance mutations to either component. The drugs are available as separate extended-release injectable suspensions for intramuscular (IM) administration, and as individual oral tablets for an optional lead-in period and/or for oral bridging of missed/late injections.[4] A summary of drug characteristics is provided in **Table 1**.[4,5]

What is the evidence? Landmark trials examining the use of cabotegravir/rilpivirine as maintenance therapy in virally suppressed patients are summarized in **Table 2**.[6-8] Cabotegravir/rilpivirine was found to be non-inferior to continuing oral ART, with over 93% of participants in either arm maintaining viral suppression at 48 weeks. The presence of at least two of the following baseline characteristics was associated with a higher risk of virologic failure: HIV-1 subtype A6/A1 (common in eastern Europe, particularly Russia), rilpivirine-associated mutations, or body mass index (BMI) ≥ 30.[9]

In a recent update from the IAS-USA guidelines panel,[10] cabotegravir/rilpivirine can be used, in certain circumstances, in patients with a detectable viral load.[11] This can be particularly beneficial if patients have difficulty accessing or being adherent to oral ART. Only limited data are available in pregnancy. If a person becomes pregnant while on cabotegravir/rilpivirine, a shared decision should be made regarding continuing the regimen with more frequent viral load monitoring, or switching to a preferred/alternate three-drug oral ART regimen for the duration of pregnancy.[12]

Dosing Oral cabotegravir 30 mg and rilpivirine 25 mg daily may be used as an optional, one-month lead-in period to assess tolerability prior to starting injections, or to bridge therapy if an injection appointment is late or missed. Since cabotegravir and rilpivirine are usually well tolerated, most practitioners now skip the oral lead-in phase.

The injection schedule includes an initiation phase with cabotegravir 600 mg/rilpivirine 900 mg given monthly for two months, followed by maintenance dosing of cabotegravir 400 mg/rilpivirine 600 mg monthly or 600 mg/900 mg every two months; the latter is most commonly used due to improved convenience. At each injection visit, two ventrogluteal (or dorsogluteal) IM injections of 2 mL or 3 mL are administered at separate injection sites.[6] For individuals with a BMI ≥ 30, a longer (2-inch) needle should be used. No dosage adjustment is required for mild/moderate renal or hepatic insufficiency; no data are available in severe renal or hepatic impairment.[4]

Missed/late doses The date of the first initiation injection becomes the target date moving forward, with future scheduled injections administered +/- 7 days from the target date. For instance, if the first injection was on the 15th of the month, all subsequent injection visits should fall between the 8th and 22nd of the month. If a patient cannot receive or misses a scheduled injection, they should receive oral bridging ART and then reinitiate injections upon discussion with their healthcare provider.[4] Oral bridging can consist of oral cabotegravir and rilpivirine tablets taken daily, or the patient's previous oral ART regimen.[13]

The recent advent of new long-acting injectable antiretrovirals offers the possibility to simplify or eliminate oral pill burden and decrease dosing frequency, which can improve adherence and reduce stigma.

Side effects Injection site reactions are common and include pain/discomfort, nodules and induration; they usually last three days after each injection and may decrease in severity with subsequent doses.[6] Approaches to minimizing injection site reactions include bringing the vials to room temperature before injection, relaxing the gluteal muscle prior to injection, injecting the contents slowly and distracting the patient.[14] Over-the-counter analgesics may be used. QT prolongation can occur with rilpivirine exposures at three times the dose of oral or injected rilpivirine; therefore, it should be used with caution in combination with drugs that have a known risk of *torsade de pointes*.[15]

Drug interactions Cabotegravir is a substrate of UGT1A1 and UGT1A9, and rilpivirine is a substrate of CYP3A4. Oral and IM cabotegravir and rilpivirine are contraindicated with potent inducers of CYP3A4 and UGT1A1 or UGT1A9. Oral rilpivirine is contraindicated with proton pump inhibitors and oral cabotegravir should be spaced apart from oral cations, such as antacids or mineral supplements, to avoid chelation; these interactions are not a concern when these antiretrovirals are administered by injection.[4]

Role in HIV PrEP (pre-exposure prophylaxis) Long-acting cabotegravir 600 mg given IM bimonthly is approved in the United States for HIV prevention,[16] and received Health Canada priority review status in January 2024.[17] Studies have found cabotegravir to be superior to daily tenofovir disoproxil fumarate–emtricitabine for PrEP in men who have sex with men, and in transgender women and cisgender women **(Table 2)**.[18,19] If an individual acquires HIV while on injectable cabotegravir, detection of a new infection may be delayed, potentially leading to INSTI resistance. Therefore, a viral load should be completed prior to each cabotegravir injection. Since cabotegravir can remain in the body for up to a year or more,[16] patients who discontinue cabotegravir are advised to initiate oral PrEP within two months of the last injection if they may continue to benefit from HIV prevention methods, and should be followed quarterly for 12 months or longer.[16]

TABLE 1

Characteristics of long-acting antiretrovirals available in Canada

	Cabotegravir/Rilpivirine (CAB/RPV)[4]		Lenacapavir (LEN)[5]
Drug Class	INSTI/NNRTI		Capsid inhibitor
Half Life	Oral: CAB: 41 hours, RPV: 45 hours IM: CAB: 5.6–11.5 weeks, RPV: 13–28 weeks		Oral: 10–12 days SC: 8–12 weeks
Dose adjustment	None for mild/moderate renal/hepatic impairment Not studied in Child-Pugh C or CrCl < 30 mL/min (no adjustment with CrCl 15–30 mL/min)		None for mild/moderate renal/hepatic impairment Not studied in Child-Pugh C or end-stage renal disease
Indication	Complete regimen for HIV-1 treatment in virologically stable and suppressed patients (HIV RNA < 50 copies/mL) May be considered for patients with viremia who meet certain conditions[10]		Treatment option for HIV-1 in highly treatment-experienced patients with multidrug resistant virus who are failing current antiretroviral regimen due to resistance, intolerance or safety considerations
Age	Adults and adolescents at least 12 years of age who weigh at least 35 kg		Adults 18 years of age or older
Baseline resistance criteria	Exclusion: known or suspected resistance to cabotegravir or rilpivirine		Requirement: resistance to at least 2 antiretrovirals from at least 3 of the 4 main classes (NRTI, NNRTI, PI, INSTI)
Oral Lead-In	Optional, 28 days to assess tolerability CAB: 30 mg daily RPV: 25 mg daily with food Take last oral dose on the day injections are started		Mandatory loading dose: A) 600 mg on days 1 and 2, 300 mg on pill day 8, then first injection on day 15, or B) 600 mg on days 1 and 2, then first injection on day 2 (this regimen is approved in the US, but not yet by Health Canada)
Dose	*Monthly injection schedule:*	*Every two-month injection schedule:*	927 mg (463.5 mg/1.5 mL x 2) injected subcutaneously
Initiation	Month 1: CAB 600 mg/RPV 900 mg	Months 1 and 2: CAB 600 mg/RPV 900 mg	1st injection on day 15 (Canada) or day 2 (US simplified dosing)
Continuation/ Maintenance	Month 2 onwards: CAB 400 mg/ RPV 600 mg (+/- 7 days)	Month 4 onwards: CAB 600 mg/RPV 900 mg (+/- 7 days)	Every 26 weeks thereafter (+/- 2 weeks)
Missed/late dose	Oral: take as soon as possible if > 12 hours until next dose; otherwise skip and resume usual dosing schedule Every 2-month injection schedule (for monthly dosing, see product monograph) Unplanned missed injections by > 7 days and no oral therapy in interim: a) Missed 2nd initiation injection: • ≤ 2 months: resume injections as soon as possible • > 2 months: restart initiation schedule from Month 1 b) Missed continuation injection: • ≤ 3 months: resume as soon as possible • > 3 months: restart initiation/maintenance sequence from Month 1 Intentional/planned missed injections: start oral bridging (either CAB/RPV or previous effective ART regimen) at time of next injection; continue until the day injection dosing is resumed		Oral: If patient vomits within 3 hours, take another dose See product monograph If > 28 weeks from last injection date, restart oral lead in
Dosing: PrEP	Cabotegravir: 600 mg IM every 2 months (+/- 7 days)		Investigational: 927 mg (463.5 mg/1.5 mL x 2) SC every 6 months
Administration	Two 2 mL or 3 mL injections into gluteal muscle. 2-inch needles recommended if BMI > 30		Two 1.5 mL injections SC into the abdomen. Use of a vial access device (supplied) is required
Drug interactions	Substrate: CAB: UGT1A1/UGT1A9 (minor) RPV: CYP3A RPV is contraindicated with > single dose of dexamethasone. Absorption/chelation drug interactions (only relevant with oral lead-in): CAB: take antacids 2 hours before or 4 hours after CAB RPV: proton pump inhibitors contraindicated		Substrate: P-gp, CYP3A (minor), UGT1A1 (minor) Inhibitor: CYP3A (moderate). Caution with CYP3A4 substrates that have a narrow therapeutic window (e.g., DOACs, digoxin, systemic corticosteroids, lovastatin, simvastatin, PDE-5 inhibitors, midazolam, triazolam) Antiretrovirals which should not be co-administered with LEN: • increased LEN: atazanavir/cobicistat • decreased LEN: efavirenz, nevirapine, tipranavir/ritonavir
	Strong inducers of CYP3A4 (carbamazepine, phenytoin, phenobarbital, rifamycins, St. John's wort) are contraindicated		
Adverse effects	Injection site reactions (pain/discomfort, nodules, induration, swelling, erythema), pyrexia, headache, fatigue, mild weight increase, elevated liver enzymes, suicidal ideation		Injection site reactions, stomach upset, hyperglycemia, elevated creatinine
Access	Drug coverage may vary across provinces. Injections may be done in clinics/ physician offices, or at supported injection sites through Bayshore or external programs		Currently not supported provincially. Patient support program through Max program (Gilead) which provides medication and administration support
Appearance	Oral: 30 mg tablet, white, film-coated oval shape Injection: 2 mL dosing kits: 400 mg CAB (dark grey cap) and 600 mg RPV (light grey cap) 3 mL dosing kits: 600 mg CAB (orange cap) and 900 mg RPV (yellow cap)		Oral: 300 mg tablets, beige capsule-shaped, supplied in a 5-pill blister pack Injection: 463.5 mg/1.5 mL vial, yellow/brown solution, preservative-free. Two vials per dose
Storage/prep	CAB/RPV: Refrigerate (2–8°C) CAB (for PrEP): Store at 2–25°C Bring vials to room temperature up to 6 hours prior to injection. Once suspension is drawn up into the syringe, stable for 2 hours		Store below 30°C (room temperature) Once drawn into syringes, administer as soon as possible Protect from sunlight

BMI–body mass index; CAB–cabotegravir; CrCl–creatinine clearance; CYP–cytochrome P450 enzymes; DOACs–direct-acting oral anticoagulants; IM–intramuscular; INSTI–integrase strand transfer inhibitor; LEN–lenacapavir; NNRTI– non-nucleoside reverse transcriptase inhibitor; NRTI–nucleoside reverse transcriptase inhibitor; PI–protease inhibitor; PrEP–pre-exposure prophylaxis; RPV–rilpivirine; SC–subcutaneous

LENACAPAVIR (SUNLENCA)

Lenacapavir is a capsid inhibitor that prevents the formation of the HIV capsid, virus assembly/release and HIV capsid uptake. It is a treatment option for adults with treatment-resistant HIV, with resistance to two or more ART classes, and must be used with other antiretrovirals to form an effective regimen. Following a short mandatory oral lead-in period, lenacapavir is administered every six months via subcutaneous injection **(Table 1)**.[5]

What is the evidence? The CAPELLA trial found that in patients with multidrug-resistant HIV, those who received lenacapavir plus an optimized background regimen had a greater reduction in viral load versus those who received placebo plus an optimized background regimen.[20] At 26 weeks, more than 80% of patients receiving lenacapavir plus an optimized background regimen achieved viral suppression. Oral and injectable lenacapavir-containing regimens are also being studied in treatment-naive individuals **(Table 2)**.[21]

Dosing Oral lead-in dosing is mandatory in order to quickly achieve therapeutic concentrations. After the oral lead-in, lenacapavir is administered every six months (26 weeks) as two 1.5 mL subcutaneous injections into the abdomen **(Table 1)**. No dosage adjustment is required for mild/moderate renal or hepatic insufficiency; no data are available in severe renal or hepatic impairment.[5]

Missed/late doses The scheduled injections should be administered every 26 weeks +/- 2 weeks from the last injection. If more than 28 weeks have elapsed since the last injection, initiation with the oral lead-in needs to be repeated.[5]

Side effects The most common adverse reactions include nausea (4%) and injection site reactions (65%). Most are mild-moderate in severity and resolve in an average of five days; nodules and indurations at the injection site may take longer to resolve (148 and 70 days, respectively).[5,22]

Drug interactions Lenacapavir is a CYP3A4 substrate and is contraindicated with potent CYP3A4 inducers. It is also a moderate CYP3A4 inhibitor; caution is advised when co-administering with sensitive CYP3A4 substrates with a narrow therapeutic index (e.g., phosphodiesterase-5 inhibitors, direct-acting anticoagulants, ergot agents, certain statins). The inhibiting effects of lenacapavir may persist for up to nine months after the last injection.[5]

Role in HIV PrEP Lenacapavir is being investigated for PrEP in various populations at risk of acquiring HIV, including adolescents and young girls, cisgender women, gay/bisexual/gender diverse men who have sex with men, and people who inject drugs **(Table 2)**.[23-26]

APPROPRIATE CANDIDATES FOR INJECTABLE ANTIRETROVIRAL THERAPY

Patients may desire long-acting therapy for a variety of reasons, including reduced/elimination of daily pill burden, increased discretion, reduced stigma or reminder of disease, enhanced regimen potency, management of swallowing/absorption difficulties and avoidance of drug interactions. People who may be appropriate candidates for injectable ART are those who are able to attend regular appointments for injections and follow-up tests; with cabotegravir/rilpivirine, these visits may be more frequent than what patients on stable oral ART may be used to.

Patients who may not be ideal candidates for long-acting ART include those who fear needles, are unable to regularly attend appointments or who have challenges adhering to oral therapy (i.e., an optimized background regimen with lenacapavir), are on a contraindicated co-medication, or have other risk factors for virologic failure. Patients with hepatitis B will need additional anti-hepatitis B virus therapy. When discontinuing injections, appropriate oral ART should be started by what would have been the next scheduled injection date.

PHARMACIST'S ROLE WITH INJECTABLE ART

The pharmacist plays a crucial role in injectable ART access, administration and adherence.[4,5]

- Pharmacists can be instrumental in advocacy and ensuring access to these drugs, often referring patients and prescribers to patient support programs if private or provincial programs do not cover the medications.
- Adherence support is important in order to minimize the risk of resistance. In particular, lenacapavir is not a complete regimen and adherence to the oral backbone therapy is critical. Ensure patients attend injection appointments and manage missed or late injection doses appropriately.
- Long-acting antiretrovirals could potentially be administered by community pharmacists; additional training for IM gluteal injection of cabotegravir/rilpivirine may be required. Ensure the injection space provides adequate privacy and patient comfort; an exam room table is recommended for gluteal injections.
- Drug interactions are a source of concern; CYP3A4 and UGT1A1/1A9 inducers are contraindicated. HIV-specific databases with practical management strategies are available through *HIV Drug Interactions* (Liverpool)[27] and the Canadian-specific *HIV/HCV Drug Therapy Guide*.[28]
- Some community pharmacists offer HIV testing or comprehensive oral PrEP programs, which may be adapted for injectable PrEP modalities.

SUMMARY

Cabotegravir/rilpivirine and lenacapavir are new long-acting injectable therapies that represent revolutionary advances in the HIV landscape. They have different roles in treatment: cabotegravir/rilpivirine allows people to be completely free of oral antiretroviral pills, while lenacapavir is a novel therapeutic agent for people with limited treatment options and must be used with other oral antiretrovirals. Cabotegravir and lenacapavir injections also represent exciting alternatives to oral HIV PrEP strategies. Development of additional long-acting agents and delivery modalities continues to be a priority for HIV medicine, with the hope of offering patients more choices throughout the prevention and treatment spectrum.

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Table 2 and References
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Table 2 and references

TABLE 2

Treatment and Prevention Studies with Long-Acting Antiretrovirals

	Cabotegravir/Rilpivirine (CAB/RPV): Treatment			Cabotegravir: Pre-exposure prophylaxis (PrEP)	
Study	**ATLAS[6]**	**FLAIR[7]**	**ATLAS-2M[8]**	**HPTN 083[18]**	**HPTN 084[19]**
Intervention	CAB/RPV vs standard of care		CAB/RPV every other month vs CAB/RPV monthly	Long-acting cabotegravir vs daily oral TDF/FTC	
Population	n=308	n=631	n=523	n=4,570	n=3,324
Dose (IM):	CAB 400 mg/RPV 600 mg once monthly		CAB 600 mg/RPV 900 mg every 2 months	CAB 600 mg every 8 weeks	
Primary endpoint	92.5% vs 95.5% with VL < 50 copies/mL at week 48	93.6% vs 93.3% VL < 50 copies/mL at week 48	94% vs 93% VL < 50 copies/mL at week 48	RR: HIV infection rate 66% lower with CAB compared to TDF/FTC	RR: HIV infection rate 88% lower with CAB compared to TDF/FTC
Achieved outcome?	Yes, non-inferiority.			Yes, superiority. Trial stopped early due to benefit	
Main adverse effects	ISRs: 75%–86%. Fever, fatigue and headache were also common.			ISRs: 81%	ISRs: 38%
Lenacapavir					
	Treatment-experienced		**Treatment-naïve**	**Pre-exposure prophylaxis (PrEP)**	
Study	**Capella[20]**		**Calibrate[21]**	**PURPOSE 1, 2, 3 and 4**	
Intervention	LEN + OBR vs OBR		Group 1/2: LEN + FTC/TAF (28 weeks following 1st injection), then just TAF or BIC Group 3: LEN oral + FTC/TAF Group 4: BIC/TAF/FTC as control	Long-acting lenacapavir vs. daily oral TDF/FTC	
Population	n=72		n=182	PURPOSE 1 (phase 3):[23] adolescents and young girls at risk of HIV (n=5,639) PURPOSE 2 (phase 3):[24] those at risk of HIV (target n=3,000) PURPOSE 3 (phase 2):[25] cis-gender women at risk of HIV (target n=250) PURPOSE 4 (phase 2):[26] people who inject drugs (target n=250)	
Dose	927 mg every six months		Group 1/2: 927 mg every six months Group 3: 4-pill lead in, then 50 mg daily thereafter.	Oral lenacapavir 600 mg (Days 1 & 2) and lenacapavir 927 mg SC on Day 1 and Week 26	
Proportion who maintained virally suppressed	81% (treatment-experienced patients)		Group 1: 90% Group 2/3: 85% Group 4: 92%	To be determined: trials are currently active/recruiting participants	
Achieved outcome?	Yes, 88% had a 0.5 log reduction in viral load in LEN + OBR arm vs 17% OBR by day 15.		Yes, efficacy (viral suppression) and safety were outcomes		
Follow up	26 weeks		54 weeks (duration at least 80 weeks)		
Main adverse effects	ISRs 62%; also nausea, constipation, diarrhea, abdominal distention, and arthralgia		ISRs; headache and nausea		

BIC–bictegravir; CAB–cabotegravir; FTC–emtricitabine; IM–intramuscular; ISRs–injection site reactions; LEN–lenacapavir; OBR–optimized background regimen; PrEP–pre-exposure prophylaxis; RPV–rilpivirine; RR–relative risk; TAF–tenofovir alafenamide; TDF–tenofovir disoproxil fumarate; VL–viral load

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