December 2022

LANCET LABORATORIES Zimbabwe

Newsletter

HIV INTEGRASE INHIBITORS

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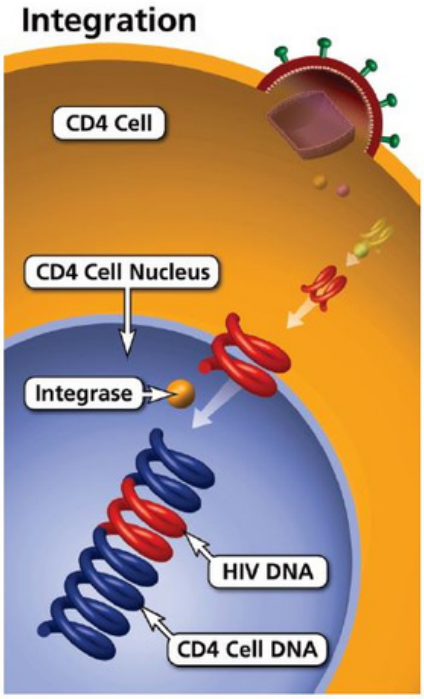
HIV Integrase Inhibitors: Their role in Clinical management

Introduction:

Clinicians now have five classes of antiretroviral agents (ARVs) for the treatment of HIV infection in both treatment-naïve and treatment - experienced individuals.

1. Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)
2. non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)
4. Entry and fusion inhibitors
5. Integrase strand transfer inhibitors (INSTIs)



Integrase strand transfer inhibitors, often abbreviated to "integrase inhibitors", target an enzyme called Integrase, a protein essential for HIV replication. As a result, proviral DNA is unable to insert into the host cell genome. This terminates the life cycle of the virus (see figure on the right).

Three INSTI's have been approved by the FDA: Raltegravir (Isentress), Dolutegravir (Tivicay) and elvitegravir (Vitekta). Raltegravir (RAL) and Dolutegravir (DTG) is registered and av**ailable for routine use in South Africa and will be the focus of this clinical update.**

Pharmacokinetics

Integrase inhibitors are well absorbed from the upper gastrointestinal tract, and rapidly achieve plasma levels that inhibit viral replication. The antiviral activity of INSTI's is primarily related to trough levels. These are usually well maintained with routine dosing regimens and are largely unaffected by concomitant food ingestion. The HIV-1 viral load declines rapidly using fully active regimens that include an INSTI; a significant proportion of individuals achieve a viral load of < 50 copies/mL within 4 weeks of commencing therapy.

RAL and DTG are primarily metabolized by Glucuronidation in the liver. There is minimal renal elimination; therefore, no dosage adjustment is necessary in patients with renal impairment. Data, however, are lacking on the use of RAL and DTG in individuals on renal dialysis and patients with severe hepatic impairment.

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Clinically significant drug interactions

AGENT	RALTEGRAVIR	DOLUTEGRAVIR
Efavirenz	No significant interaction	No significant interaction
Etravirine	No significant interaction	Avoid
Nevirapine	No significant interaction	Avoid
Rilpivirine	Preferably avoid combination; Use rifabutin instead of rifampicin. In treatment-naïve individuals RAL 800 mg bid may be considered	No significant interaction
Cationic antacids, calcium and iron supplements	Administer RAL 2 hours before, or 6 hours after	Administer DTG 2 hours before, or 6 hours after
Rifampicin	Preferably avoid combination; use rifabutin instead of rifampicin. In treatment-naïve individuals RAL 800 mg bid may be considered	Increase DTG dose to 50 mg bid
Rifabutin	No significant interaction	No significant interaction
Carbamazepine, Phenytoin	Unknown	Avoid

- The half-life of RAL necessitates twice-daily dosing whereas DTG can be administered as a single daily dose.

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Resistance

Understanding RAL and DTG resistance mechanisms can help optimize their clinical use. Resistance has been well-described for all INSTI's but occurs more readily with RAL and Elvitegravir (which largely share resistance profiles) than DTG. The primary factors driving INSTI resistance are poor patient adherence and the prescription of suboptimal medication combinations.

Major Primary INSTI Resistance Mutations

	T	E	E	G	Y		Q	N		
Raltegravir	66	92	138	140	143		148	155		
	A	Q	KA	SA	RCH		HRK	H		
	T	E	E	G		S	Q	N		
Elvitegravir	66	92	138	140		147	148	155		
	IAK	Q	KA	SA		G	HRK	H		
		E	E	G			Q		R	
Dolutegravir		92	138	140			148		263	
		Q	KA	SA			HRK		K	

Mutations in **ORANGE** associated with highest levels of reduced susceptibility or response.
Mutations in **YELLOW** reduce INSTI susceptibility or response.

Adapted from the Stanford HIV Drug Resistance Database.

Treatment failure within the first 6–12 months of RAL use is typically associated with the emergence of the N155H mutation, with or without secondary mutations. Viruses harboring this primary mutation are usually susceptible to DTG, permitting sequential use. In these cases, DTG at the higher dose of 50 mg bid should be prescribed as treatment.

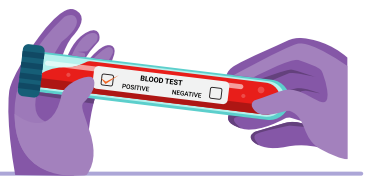
Failure after 12 months of RAL use is frequently due to the emergence of viruses that harbor the Q148H/R/K mutation, with or without secondary mutations. These viruses are invariably resistant to DTG as well. When DTG is used as the first INSTI, emergence of resistant viral populations is rare. The Q148H/R/K mutation markedly impairs viral fitness.

Testing for integrase inhibitor resistance

With the start of the use of INSTIs in South Africa, there will be the inevitable development of INSTI resistance. As a result of this, Lancet Laboratories have developed and validated an **Integrase Inhibitor Resistance Assay**.

Requirements for the Integrase Inhibitor Resistance Assay:

- The individual must be experiencing virological failure (HIV-1 viral load greater than 1 000 copies/mL)
- The individual must be taking the INSTI at the time of ordering the HIV Integrase Resistance Test
- Please state clearly on the request form that HIV Integrase resistance testing should be included as it does not form part of the normal, routine HIV resistance test
- Two EDTA (purple top) tubes are required



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