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NEWSLETTER

HIV INTEGRASE INHIBITORS: THEIR ROLE IN CLINICAL MANAGEMENT

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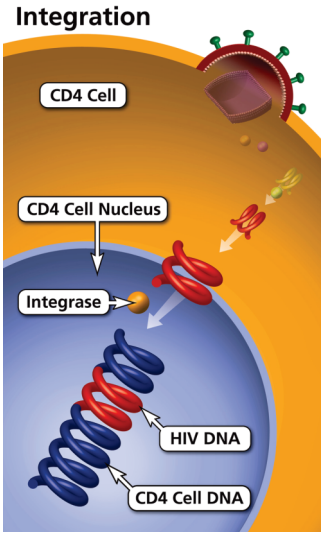
4th Quarter 2016

Introduction

Clinicians now have five classes of antiretroviral agents (ARVs) for 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 INSTIs have been approved by the FDA: raltegravir (*Isentress*), dolutegravir (*Tivicay*) and elvitegravir (*Vitekta*). Raltegravir (RAL) and dolutegravir (DTG) are registered and available 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 INSTIs is primarily related to trough levels. These are usually well maintained with routine dosing regimens and are largely unaffected by concomitant ingestion of food. 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 metabolised 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.

Potentially significant drug interactions are shown in the Table 1.

Table 1. Clinically significant drug interactions

AGENT	RALTEGRAVIR	DOLUTEGRAVIR
Efavirenz	No significant interaction	Increase DTG dose to 50 mg bid
Etravirine	No significant interaction	Avoid
Nevirapine	No significant interaction	Avoid
Rilpivirine	No significant interaction	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.

Significant side effects

INSTIs are generally well-tolerated with few side effects, headache and gastrointestinal effects being most common (2% – 6% of patients). Other nervous system (including neuropsychiatric) effects (e.g. insomnia) have been reported with INSTIs but are milder and less frequent than with efavirenz. Limited data suggest that effects upon lipid metabolism with RAL and DTG are favourable compared with efavirenz and protease inhibitors. DTG has been shown to increase the serum creatinine due to reduced tubular excretion; this occurs in the absence of reduced glomerular filtration. Rare and severe adverse events possibly related to INSTIs include extensive rash, systemic hypersensitivity reactions and rhabdomyolysis.

Clinical studies

Several large international studies have been performed to assess the use of RAL and DTG in first- and second-line treatment regimens.

- *RAL in first-line:* STARTMRK evaluated the use of RAL in treatment-naïve individuals. STARTMRK had two treatment arms RAL (twice daily) with FTC/TDF versus EFV with FTC/TDF and found that the RAL arm was non-inferior to the EFV arm after 48 weeks. Elvitegravir has also been shown to be non-inferior compared to an EFV-based arm and PI-based arm in treatment-naïve individuals.
- *RAL in second-line:* The published ERNEST , SECOND-LINE and SELECT studies have all found that treatment with RAL and lopinavir/ritonavir (LPV/r) is non-inferior to 2 NRTIs and LPV/r after 48 weeks on treatment. The SECOND-LINE study found that at week 48 there was a difference of 1.8 % between the two arms. Of the subjects that experienced virological failure in the RAL arm, 14.9 % had mutations linked to reduced susceptibility to RAL.
- *DTG in first- and second-line:* Dolutegravir has shown to be effective in both treatment-naïve and treatment-experienced individuals. DTG is the only INSTIs to show non-inferiority with secondary superiority in the SINGLE study when compared to EFV. In the FLAMINGO study (DTG versus DRV/r in treatment-naïve individuals), individuals taking DTG once daily were found to have a better viral response compared to those taking DRV/r and compared well from a safety perspective. Similar results were observed with the SPRING study when DTG was compared to RAL in treatment-naïve individuals. Of interest, no integrase resistance was reported in either the SINGLE or FLAMINGO studies and the development of resistance is extremely rare in treatment-experienced individuals and is linked to non-adherence. DTG was the first anti-retroviral agent to show superior virological efficacy over RAL in treatment-experienced patients in the SAILING study.

Resistance

Understanding RAL and DTG resistance mechanisms can assist to optimize their clinical use. Resistance has been well-described for all INSTIs, 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 prescription of suboptimal medication combinations (see below).

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 harbouring this primary mutation are usually susceptible to DTG, permitting sequential use. In these cases DTG should be prescribed at the higher dose of 50 mg bid. Treatment failure after 12 months of RAL use is frequently due to the emergence of viruses that harbour 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.

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.

Clinical use of INSTIs

- In South Africa, INSTIs are generally reserved for the treatment of patients who are treatment-experienced and who are failing their current regimen. In this context, RAL or DTG must be used with ***at least*** boosted darunavir (darunavir 600 mg bid PLUS ritonavir 100 mg bid; DRV/r), preferably with DRV/r AND one or more active agent/s based on the results of an HIV resistance test. Healthcare providers should seek the advice of an experienced colleague when constructing such a regimen.
- In many other parts of the world, INSTIs are now regarded as preferred drugs for initial therapy. They are typically combined with either tenofovir/FTC, tenofovir/3TC or abacavir/3TC. The fixed drug combination of abacavir 600 mg/3TC 300 mg/dolutegravir 50 mg (*Trelavue*, 1 tablet once daily) is now available in South Africa for initial antiretroviral therapy.

  PLEASE NOTE: Patients should be screened for the abacavir hypersensitivity marker HLA B*5701 prior to prescribing any abacavir-containing regimen, including *Trelavue*.
- Note that a patient failing an initial efavirenz- or nevirapine-containing regimen should not be switched to an INSTI-containing combination without ensuring that the viral population remains susceptible to the other two components of the regimen; i.e. an HIV resistance test should be performed. Failure to do so greatly increases the risk of INSTI resistance.
- RAL and DTG appear to be safe in pregnancy although no formal studies have been done.
- RAL can be used to treat infants and children aged ⩾ 4 weeks and weighing ⩾ 3 kg; specific paediatric dosing guidelines are available. DTG is not yet approved for use in infants, but studies are ongoing. Dosing guidelines are available for children weighing ⩾ 30 kg.

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

Suggested reading

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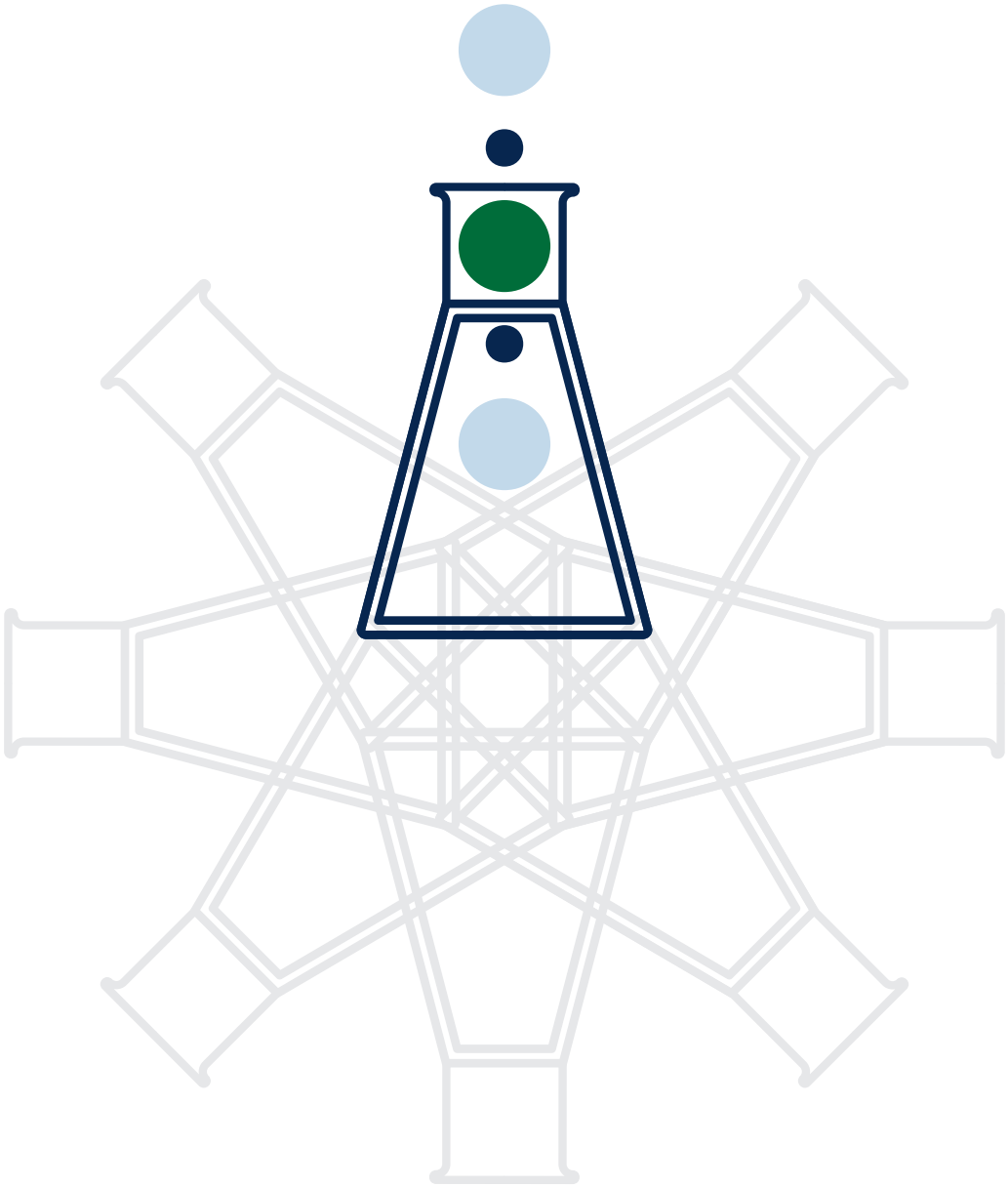

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ITEM CODE: N00161

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