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Pharmacokinetic Properties and Resistance Profiles of the Integrase Inhibitors: Clinical Implications in the Treatment of HIV Infection

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This review article compares the pharmacokinetic properties and resistance profiles of the three integrase strand transfer inhibitors currently registered in NZ for the treatment of HIV infection in adults and discusses how these characteristics might translate into clinical advantages or disadvantages for patients. This review is sponsored by GlaxoSmithKline (NZ) Ltd.

Role in antiretroviral therapy

Antiretroviral therapy (ART) is the mainstay of the prevention and treatment of HIV infection and is recommended for almost all HIV-infected individuals as soon as possible following diagnosis, according to the 2018 International Antiviral Society-USA Panel (IAS-USA) recommendations for the use of ART for HIV infection in adults.[1] A combination of an integrase strand transfer inhibitor (INSTI) plus two nucleoside reverse transcriptase inhibitors is generally recommended for first-line therapy, with patient-specific characteristics guiding the treatment selection.

In addition to their important role in the treatment of ART-naïve patients, INSTIs retain potency against HIV strains that are resistant to other classes of antiretroviral agents such as non-nucleoside reverse transcriptase inhibitors and protease inhibitors hence making them a novel treatment option for patients with acquired and transmitted resistance to other antiretroviral classes.[2]

Three INSTIs are currently approved for treatment of HIV infection in NZ: dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL).[3-5] DTG and RAL are marked and funded (under special authority). DTG is also registered (but not yet marketed) as dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) fixed-dose combination tablet. EVG is registered (but not yet marketed) as elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine (EVG/COBI/TDF/FTC) fixed-dose combination tablet. An advantage of co-formulated tablets is that they allow for convenient and simplified ART regimens,[2] which may facilitate patient adherence to treatment.

Clinical efficacy and tolerability

DTG, EVG, and RAL have demonstrated virological efficacy in both treatment-naïve and treatment-experienced HIV-infected patients that is equivalent or superior to previously preferred treatments.[7-12]

In head-to-head studies, the virological efficacy of DTG was non-inferior to that of RAL in treatment-naïve patients and superior to that of RAL in treatment-experienced patients.[13,14] EVG and RAL demonstrated similar efficacy in treatment-experienced patients.[15] Regarding tolerability, DTG, EVG, and RAL have been generally well tolerated in clinical trials in both treatment-naïve and treatment-experienced patients.[7-9,11,12] In head-to-head studies of EVG versus RAL and DTG versus RAL the tolerability profiles of the INSTIs were generally comparable.[13-15]

While DTG, EVG, and RAL are similar in terms of efficacy and tolerability there are differences with regard to their pharmacokinetic properties and resistance profiles that have potential clinical relevance for the individualisation of patient care.

Pharmacokinetic properties

Relevant pharmacokinetic characteristics of DTG, EVG, and RAL are summarised in **Table 1**. In addition to having similarities, each INSTI has certain unique pharmacokinetic properties that result in different dose, food, booster requirements, and drug-drug interaction (DDI) profiles, and can have implications for certain patient groups.[2]

In pharmacokinetic studies, RAL has demonstrated substantially higher degrees of intra- and interpatient variability in pharmacokinetic parameters compared with the other INSTIs.[2] DTG has demonstrated relatively low absorption pharmacokinetic variability compared with other INSTIs,[2] which may indicate greater stability of its plasma concentration in patients.

Absorption

DTG, RAL, and EVG are rapidly absorbed following oral administration with the time taken to reach peak plasma concentration (T_{max}) ranging from 2 to 4 hours post-dose.[3,5,16] Low-fat and high-fat meals increase the bioavailability of the three INSTIs and, while it is recommended that EVG should be administered with food, both DTG and RAL can be administered with or without food.[3-5]

Distribution

DTG, EVG, and RAL are extensively bound to human plasma proteins (83–99%) following absorption,[3-5] which likely will help to minimise drug removal in HIV-infected patients undergoing renal replacement therapy.[2]

Metabolism and elimination

DTG and EVG exhibit elimination half-lives ($t_{½}$) of approximately 14 hours and 13 hours, respectively, and are both administered once-daily in treatment-naïve HIV-infected patients while RAL, with a $t_{½}$ of 9 hours, is administered twice-daily.[3-5] Once-daily dosing may lead to better adherence compared with twice-daily administration.[17]

DTG, EVG, and RAL are primarily metabolised and eliminated by the liver.[3-5] An important distinguishing characteristic of the INSTIs is the difference in their pathways of hepatic metabolism: EVG is primarily metabolised by cytochrome P450 3A4 (CYP3A4) while DTG and RAL are primarily metabolized by uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1).[2] Additionally, EVG must be given with a pharmacokinetic booster, cobicistat (COBI), to achieve systemic exposure that enables once-daily dosing, and COBI is also mainly metabolised by CYP3A4.[5,18] Consequently, EVG/COBI has a higher propensity to cause DDIs than DTG and RAL (see **Drug Interactions** section). Regimens not requiring pharmacological boosting are preferred in the 2018 IAS-US recommendations for initial ART.[1]

DTG inhibits the tubular secretion of creatinine by inhibiting renal organic cation transporter 2, OCT2, in the proximal tubules, which is the mechanism underlying the mild increases in serum creatinine levels observed in HIV-infected patients treated with DTG.[2,4] However, these changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate.[4]

Special populations

The unique pharmacokinetic characteristics of the three currently registered INSTIs can have implications for certain patient-population conditions, including renal and hepatic impairment, co-infections, and pregnancy.[2]

Renal impairment

As renal clearance is a minor pathway of elimination for DTG, EVG, and RAL, kidney disease is not expected to significantly influence systemic exposure to these INSTIs.[2-5] Hence, no dosage adjustment is necessary for patients with mild, moderate, or severe renal impairment.

However, the EVG/COBI/TDF/FTC co-formulated tablet is not recommended for initial therapy in patients with an estimated creatine clearance (CL_{CR}) ≤70 mL/min due to FTC and TDF being primarily excreted by the kidney.[2,5] Routine monitoring of estimated CL_{CR} should be performed during treatment with EVG/COBI/TDF/FTC, with falls below 50 mL/min necessitating discontinuation of EVG/COBI/TDF/FTC because dose-interval adjustment required for FTC and TDF is not possible with the fixed-dose combination tablet. EVG/COBI/TDF/FTC may be used for patients with moderate renal insufficiency (CL_{CR} 30–69 mL/min).

In a study of the pharmacokinetics of COBI-boosted EVG, no clinically-relevant differences in EVG or COBI pharmacokinetics were observed in patients with severe renal impairment and healthy controls.[5] Although COBI may cause modest increases in serum creatinine and modest declines in estimated CL_{CR} (due to inhibition of the tubular section of creatinine) without affecting renal glomerular function, patients who experience an increase in serum creatinine of >0.4 mg/dL from baseline should be monitored for renal safety.

Although dose-reduction of DTG is not required in patients with severe renal impairment and without INSTI resistance, caution is warranted with the use of DTG in patients with severe renal impairment and known or suspected INSTI resistance mutations, as reduced DTG systemic exposure may result in loss of therapeutic effect and development of resistance.[4] In addition, similar to COBI, DTG can cause an increase in serum creatinine levels and reductions in estimated CL_{CR} due to inhibition of the tubular secretion of creatinine without affecting renal glomerular function. Therefore, reductions in estimated CL_{CR} should be considered when DTG is co-administered with drugs that have dosing adjustment recommendations guided by estimated CL_{CR}.

Regarding the effect of renal replacement therapy on INSTI pharmacokinetics, removal of DTG, EVG and COBI, and RAL is expected to be minimal due to these agents being highly bound to plasma proteins (83, 98-99 and 97-98, and 99% binding, respectively).[2-5]

Hepatic impairment

Liver disease can influence the pharmacokinetics of antiretroviral agents due to changes in liver blood flow or shunting, altered synthesis of plasma proteins, and metabolism via cytochrome enzymes and glucuronidation.[2]

Although DTG, EVG and COBI, and RAL are primarily metabolized and eliminated by the liver, no clinically-relevant differences in the pharmacokinetics of these agents in patients with moderate hepatic impairment and healthy controls have been demonstrated.[2-5] Hence, these agents may be used at standard doses in patients with mild-to-moderate hepatic impairment (Child-Pugh class A or B).

The effect of severe hepatic impairment (Child-Pugh class C) on the pharmacokinetics of DTG, EVG and COBI, and RAL has not been studied.

Table 1. Comparison of the pharmacokinetic characteristics of the INSTIs.[3-5,16,19,20]

	DTG	EVG[a]	RAL
Administration			
Dose	50mg	150mg	400mg
Frequency	Once daily[b]	Once daily	Twice daily
Absorption			
C_{max}	3.7 µg/mL	1.7 µg/mL	NC
AUC	53.6 µg•h/mL	23.0 µg•h/mL	NC
C_{trough}	1.11 µg/mL	0.45 µg/mL	NC
T_{max}	≈2–3h	≈4h	≈3h
Effect of low-fat meal[c]	↑33%	↑36%	↑46%
Effect of high-fat meal[c]	↑66%	↑91%	↑100%
Distribution			
Binding to human plasma proteins	≈99%	≈99%	≈83%
Metabolism			
Pathway	UGT1A1 (major) CYP3A (minor)	CYP3A (major) UGT1A1/3 (minor)	UGT1A1 (major) CYP3A (minor)
Excretion			
$T_{1/2}$	≈14h	≈13h	≈9h
Major route of elimination	Metabolism	Metabolism	Metabolism
Proportion of dose excreted in urine	31%	6.7%	32%
Proportion of dose excreted in faeces	53%	94.8%	51%

a EVG as EVG/COBI/TDF/FTC fixed-dose combination tablet.
b Some patients may require twice-daily dosing; please refer to the DTG Data Sheet before prescribing.
c Expressed as AUC relative to fasting.
Abbreviations: AUC = area under the concentration-time curve; COBI = cobicistat; C_{trough} = minimum concentration; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; h = hours; NC = not calculated; RAL = raltegravir; TDF = tenofovir disoproxil fumarate; $T_{1/2}$ = terminal plasma half-life; T_{max} = time to maximum plasma concentration.

Pregnancy

The 2018 IAS-USA recommendations state that ART should be initiated in HIV-infected women who are pregnant as soon as possible, not only for their own benefit but also to prevent HIV transmission to the infant.[1] INSTIs have an important role to play in managing HIV infection during late pregnancy because of the rapid reduction in retroviral load achieved with INSTI therapy.[2] However, induction of CYP3A4 and UGT1A1 during pregnancy has the potential to affect INSTI metabolism and necessitate dose adjustment.

In the 2018 IAS-US recommendations, RAL is the preferred INSTI option in the treatment of HIV-infected women who are already pregnant.[1] According to the RAL prescribing information, RAL 400mg twice daily may be considered during pregnancy, if clinically needed.[3]

A preliminary analysis of data from an observational surveillance study of birth outcomes among pregnant women on ART in Botswana identified four cases (0.94%) of neural tube defects in 426 infants born to women taking a DTG-based regimen at conception.[21] No neural tube defects were observed in infants born to women who started DTG during pregnancy (n=2812). A subsequent analysis of the study data identified no new neural tube defects in 596 infants born to women taking pre-conception DTG, providing an updated prevalence of 0.67%.[22] On the basis of the preliminary report, the 2018 IAS-USA recommendations suggest that DTG should be avoided in women of childbearing age who wish to become pregnant, are trying to get pregnant, or are sexually active and not reliably using contraception.[1] Currently, it is unclear whether other INSTIs present a similar risk of neural tube defects.

The prescribing information for DTG recommends that it should be used in pregnancy only if the expected benefit justifies the potential risk to the foetus.[4] Women of childbearing age should undergo pregnancy testing prior to starting DTG, and DTG should be avoided in the first trimester.[4] Effective contraception should be used for the duration of their treatment with DTG.

As there are no well controlled clinical studies of EVG/COBI/TDF/FTC in pregnant women, and because animal reproductive studies are not always predictive of human response, the prescribing information recommends that EVG/COBI/TDF/FTC should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.[4] The 2018 IAS-US recommendations currently do not endorse COBI-boosted EVG for use during pregnancy.[1]

Co-infection

Pharmacokinetic data in healthy volunteers and patients co-infected with HIV and tuberculosis indicate reductions in systemic exposure of RAL when it is given in combination with rifampicin (see **Drug interactions**),[2] Hence, caution is recommended when co-administering RAL with rifampicin.[3]

Rifampicin also reduces systemic exposure of DTG such that the recommended dose of DTG is 50mg twice daily when co-administered with rifampicin (see **Drug interactions**).[4] Preliminary data from the randomised open-label INSPIRING trial suggest that DTG 50mg twice daily is an effective and well-tolerated treatment in ART-naïve patients with HIV/TB co-infection receiving rifampicin-based TB therapy.[23]

Co-administration of rifampicin with EVG is contraindicated due to reduced systemic exposure of EVG and potential loss of virologic response (see **Drug interactions**).[5]

Studies evaluating INSTI therapy in patients co-infected with HIV and hepatitis C virus (HCV) are lacking; however, DDI data in healthy volunteers suggest minimal effects of the newer direct-acting antivirals on the pharmacokinetics of RAL and DTG.[2] In addition, population pharmacokinetic analyses suggest that HCV co-infection has no clinically-relevant effect on systemic exposure of DTG or boosted EVG.[4,5]

Dug-drug interactions

The different metabolic pathways of INSTIs can lead to differences in the potential for DDIs.[2,18]

DTG and RAL have a low propensity to cause clinically-relevant DDIs because their metabolism requires minimal cytochrome involvement.[2,18] In contrast, EVG has a higher propensity to cause DDIs due to being primarily metabolised by CYP3A4 and requiring pharmacokinetic boosting with COBI, which is also strongly metabolised by CYP3A4.

RAL is mainly metabolized by UGT1A1-mediated glucuronidation and is not an inhibitor of UGT or P-glycoprotein (P-gp)-mediated transport, which contributes to its low propensity to cause DDIs.[3,18] However, co-administration of RAL with potent drug-metabolising inducers such as rifampicin, which is a UGT1A1 inducer, results in reduced RAL plasma concentrations.[2,3,18] Hence, caution is advised when RAL is administered concurrently with rifampicin or other potent inducers of UGT1A1.[3]

DTG also has a low propensity for DDIs due to being primarily metabolized by UGT1A1 (with minor metabolism by CYP3A4) and being a minor inhibitor and minor inducer of metabolic pathways.[4,18] However, DTG is a substrate of UGT1A3, UGT1A9, breast cancer resistance protein (BCRP), and P-gp. Hence, DTG dosage modification may be required to maintain therapeutic effect or minimise toxicity in patients using medications that induce or inhibit these enzymes. Also, co-administration of DTG and metformin increases metformin plasma concentrations dose-dependently due to DTG-mediated inhibition of renal OCT2. A dose adjustment of metformin should be considered when commencing and ceasing administration of DTG in HIV-infected patients receiving metformin to maintain glycaemic control.[4] Presumably due to its induction effect on UGT1A1,[2] rifampicin has been shown to reduce DTG availability leading to reduced plasma DTG concentrations.[4] Hence, the recommended dose of DTG is 50mg twice daily when co-administered with rifampicin.

There is a higher risk of DDIs occurring with COBI-boosted EVG than with either DTG or RAL, mainly because EVG and COBI are both metabolised by CYP3A and COBI also being metabolised by CYP2D6, although to a lesser extent.[5,17] Inhibitors (such as ketoconazole and ritonavir) or inducers (such as rifampicin, phenytoin, and carbamazepine) of these pathways can alter EVG plasma concentrations, potentially resulting in loss of therapeutic activity or toxicity.[5,17] Hence, co-administration of COBI-boosted EVG with these drugs is either contraindicated or requires clinical monitoring.[5] For example, co-administration rifampicin with EVG is contraindicated due to rifampicin being a strong CYP3A inducer. In addition, as COBI inhibits the transporters P-gp, BCRP, human organic anion transporting polypeptide (OATP) 1B1 and OATP1B3, the co-administration of COBI-boosted EVG with drugs that are substrates of P-gp, BCRP, OATP1B1, or OATP1B3 may result in increased plasma concentrations of these drugs.[5]

Co-administration of DTG, EVG, or RAL with medications that contain polyvalent metal cations (e.g. Al^{3+}, Ca^{2+}, Mg^{2+}, $Fe^{2+/3+}$ may impair absorption by chelation, resulting in reduced plasma INSTI concentrations.[3-5] These DDIs can be avoided by dose separation.[2]

TAKE-HOME MESSAGES - PHARMACOKINETICS

- **The different PK properties and resistance profiles of the INSTIs may suit different clinical scenarios and individual patient circumstances in the treatment of HIV infection.**
- **EVG can be given once daily but requires pharmacokinetic boosting and must be taken with food.**
- **RAL does not require PK boosting and can be given with or without food but requires twice-daily dosing.**
- **DTG is the only INSTI that can be given once-daily without the need for pharmacokinetic boosting and can be taken with or without food.**
- **COBI-boosted EVG is mainly metabolised by CYP3A whereas DTG and RAL are mainly metabolised by UGT1A1.**
- **The simpler metabolic profile of DTG and RAL compared with COBI-boosted EVG translates into a lower risk of DDIs with DTG and RAL.**
- **DTG, EVG, and RAL do not require dosage adjustment in renal impairment or in mild to severe hepatic impairment; however, kidney function monitoring is required with the EVG fixed-dose combination.**
- **Preliminary data suggesting a potential neural tube defect signal with DTG have raised concerns regarding the use of DTG (and potentially other INSTIs) for women of childbearing age.**

Resistance

Rates of resistance to the three INSTIs in clinical settings have been low and generally lower than with other antiretroviral classes.[24] In randomised controlled trials, treatment-emergent DTG resistance has not been identified to date in treatment-naïve HIV-infected patients but has been reported for EVG and RAL (**Table 2**).[13,25-32]

In treatment-experienced patients, statistically significantly less treatment-emergent resistance has been reported for DTG than for RAL while similar rates of resistance have been reported for EVG and RAL (**Table 2**).[14,15]

Table 2. Rates of INSTI resistance in treatment-naïve and treatment-experienced HIV-infected patients in randomised controlled trials of dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL).[13-15,25-32]

	Rates of treatment-emergent INSTI-resistance mutations	
	Treatment-naïve patients	Treatment-experienced patients
DTG	0% (n=1315; 4 trials)	1% (4/354) vs 5% (17/361) with RAL (p=0.003)
EVG	0.3–2.6% (n=2434; 3 trials)	4% (16/351) vs 4% (15/351) with RAL
RAL	1.4–1.8% (n=884; 2 trials)	5% (17/361) vs 1% (4/354) with DTG (p=0.003) 4% (15/351) vs 4% (16/351) with EVG

HIV-integrase binding

The INSTIs act by inhibiting the integrase enzyme responsible for incorporating double-stranded DNA into the host cell chromosome, which prevents HIV replication and infection of other cells.[17,33]. Indeed, the integrase enzyme released by the retroviral particle plays a critical role in HIV-1 replication and thus represents an important target for ART.[33]

By binding to the integrase active site and blocking the HIV integrase-mediated strand transfer of the retroviral DNA into the host cell DNA, which is essential for the HIV replication cycle, INSTIs interfere with the insertion of HIV-1 DNA into the host cell genome.[33] The integration process involves two consecutive integrase-catalysed reactions: (i) 3'-processing and (ii) strand-transfer. The 3'-processing reaction involves endonucleolytic cleavage at each end of the retroviral DNA, which ensures the positioning of the retroviral DNA ends in the active site necessary for the strand-transfer reaction, which catalyses the integration of retroviral DNA into the host cell genome.

The integrase enzyme released from the HIV-1 particle is a 288-amino acid protein comprised of the C-terminal domain, the N-terminal domain, and the catalytic core domain.[33,34] Most INSTI resistance mutations occur close to the integrase enzyme active site in the catalytic core domain, which is a stable dimetric organisation harbouring three highly conserved acid residues consisting of the catalytic triad (D64, D116, E152), also referred to as the DDE motif. The catalytic triad is responsible for the chelation of the two divalent metal ion co-factors (Mg^{2+}), which are required for DNA binding.

The INSTIs preferentially or specifically target the strand transfer reaction.[33] Structural and functional analyses indicate that DTG binding with HIV integrase-DNA is similar to that of EVG and RAL (Hare et al., 2011), with the three co-planar oxygen atoms allowing the chelation of the Mg^{2+} cations while the halogenated group competes with the binding of the 3'-processed end of the DNA (**Figure 1**).[33]

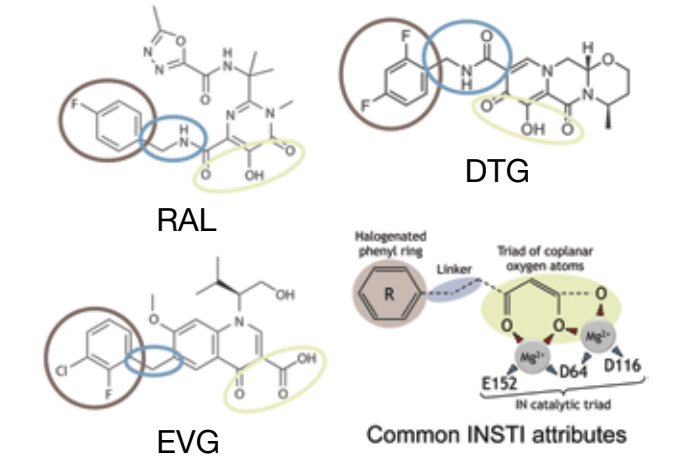

Figure 1. Mechanism of action of the INSTIs.[33] The chemical structures of DTG, EVG, and RAL with their common structural moieties are highlighted, including: (i) a triad of co-planar oxygen atoms (green) chelating a pair of divalent metal ions (Mg^{2+}); (ii) a halogenated phenyl ring (brown) invading the pocket natively occupied by the retroviral DNA extremity; and (iii) a linker (blue) of variable length and flexibility, which separates the two moieties. The integrase catalytic residues of the catalytic triad (E152, D64, D116) chelating the two Mg^{2+} cations are also indicated. The two structural moieties of the INSTIs are involved in weak interactions with the integrase residues, depending on the INSTI.

However, even though the three INSTIs are structurally related, DTG has a more streamlined chemical configuration than either EVG or RAL (**Figure 1**), with the absence of protruding functional groups allowing for a more secure fit in the integrase active-site pocket.[33] The extended linker region connecting the triad of co-planar oxygen atoms (i.e. the metal ion chelating core) and the halogenated phenyl ring of DTG allows it to penetrate farther into the pocket than EVG and RAL and to make closer contacts with retroviral DNA compared with those made by EVG and RAL. Other analyses suggest that DTG has the ability to re-adjust its position and conformation in response to structural changes in the active sites of first-generation INSTI-resistant integrases.[35]

These structural and functional observations are supported by *in vitro* data showing slower dissociation of DTG from the wild-type HIV integrase-DNA complex versus the other two INSTIs, with the dissociative half-lives being 71 hours for DTG versus 8.8 hours for RAL and 2.7 hours for EVG.[36] Prolonged binding (dissociative half-life ≥5 hours) of DTG with INSTI-resistant HIV integrase-DNA complexes was also demonstrated.

The greater intrinsic stability of DTG binding to the HIV integrase-DNA complex, as evidenced by its longer dissociative half-life, seems likely to account for the higher antiviral efficacy of DTG compared with that of RAL and EVG,[33] its higher barrier to resistance,[18] and its ability to maintain activity against EVG- and RAL-resistant mutants.[37]

WELLINGTON EXPERIENCE WITH INSTIs
– *remarks from James Rice-Davies*

As you are aware, EVG is registered but not marketed in NZ. The HIV cohort of 427 patients in the Wellington region are generally on the usual ART regimens such as a backbone of NRTIs with either an NNRTI, RAL/DTG, or a PI as the third agent.

Currently, we see very little in the way of resistance to treatment in either our naïve or our treatment-experienced patients. From memory, in the past eight years, we have had three patients who did not respond well to first-line treatment and only have a few patients with resistant patterns due to starting treatment more than a decade ago. We do however have approximately 20 patients that have difficulty taking their medication regularly due to a variety of reasons. For these patients, the general pattern appears to be good adherence for three to six months on antiretrovirals and then a break off treatment. This can have health issues although possibly fewer resistance problems than a constant poor pattern of taking antiretrovirals three or four times a week.

When we first had funded access to DTG we found the once-daily INSTI to be more convenient for patients, although recently there has been more reluctance to swap from RAL due to the CNS effects seen with DTG such as restlessness causing sleep disturbance and for a few patients a lowering of mood.

James Rice-Davies
HIV/ID Clinical Nurse Specialist Wellington Hospital

James started as a registered mental health nurse and went on to complete his general nurse training. In 1987 he started work on one of the first AIDS Units in London. He has recently completed his Masters in Nursing Science at Victoria University and has now been accepted in the Doctoral Programme at Victoria University in Wellington. His PhD thesis will examine the issues around late diagnosis and missed opportunities for HIV testing.

Barrier to resistance

Choosing a drug combination with a high barrier to resistance is considered important for initial ART according to the 2018 IAS-US recommendations, especially in the context of poor adherence to therapy.[1]

The rapid emergence of pathways involved in resistance of RAL and EVG indicate that both first-generation INSTIs have a lower genetic barrier to resistance while the susceptibility of EVG- and RAL-resistant HIV-1 mutants to DTG confirm the higher resistance barrier of DTG.[33] For example, in an *in vitro* biological characterisation study, the selection of HIV-1 resistance-associated mutations progressed at a slower rate with DTG than with EVG and DTG displayed greater antiviral activity than either EVG or RAL against a panel of 47 patient-derived INSTI-resistant HIV-1 mutant isolates with a high level INSTI resistance.[38]

The higher genetic barrier to resistance of DTG relative to the first-generation INSTIs is consistent with its higher inhibitory quotient (IQ).[18] The IQ is the ratio of the minimum concentration in a biological fluid (C_{trough}; i.e. systemic exposure) divided by the *in vitro* inhibitory concentration (IC_{50}, IC_{90}, or IC_{95}; i.e. potency), which is the quantity of INSTI achieved relative to the quantity of INSTI required to inhibit the HIV-1 virus.[2]

High IQ values infer high potency and rapid reductions in retroviral load.[2] The more rapidly that the circulating retroviral biomass is reduced the lower the likelihood of selecting for resistant mutants, which contributes to a high barrier to resistance.[39] At approved doses for the three INSTIs, the hierarchy of IQ values is: DTG (17) > EVG (10) > RAL (8),[2] which is supported by the results of comparative clinical trials showing the efficacy of DTG to be non-inferior to RAL in ART-naïve patients and superior to RAL in ART-experienced patients.[13,14]

TAKE-HOME MESSAGES - RESISTANCE

- **INSTIs work by binding to the HIV integrase active site and blocking the strand transfer step of retroviral DNA integration into the host cell genome.**
- **The greater stability of DTG binding to HIV integrase, as indicated by its longer dissociation half-life in vitro versus EVG and RAL, likely contributes its higher barrier to resistance.**
- **DTG has greater activity against INSTI-resistant mutants in vitro and achieves higher IQ values compared with EVG and RAL, indicating a higher barrier to resistance.**
- **Treatment-emergent DTG resistance has not yet been seen in treatment-naïve patients in randomised controlled clinical trials.**
- **The apparent higher resistance barrier of DTG is supported by its virological efficacy having been shown to be non-inferior to that of RAL in treatment-naïve patients and superior to that of RAL in treatment-experienced patients.**

Resource box

- AIDSource – National Institutes of Health https://aids.nlm.nih.gov/resources-for/1671/health-professionals
- Australasian Society for HIV Medicine https://www.ashm.org.au/resources/HIV-Resources/
- British Association for Sexual Health and HIV https://www.bashh.org/
- European AIDS Clinical Society http://www.eacsociety.org/eacs-resource-library/eacs-resource-library.html
- National Institutes of Health – Office for AIDS Research https://www.oar.nih.gov/hiv-resources/health-professionals
- University of Liverpool Interaction Checker https://www.hiv-druginteractions.org/

EXPERT'S CONCLUDING COMMENTS - MASSIMO GIOLA

The antiretroviral armamentarium has changed markedly since the introduction of the first protease inhibitor (PI) in the second half of the 1990s. The paradigm of triple therapy, however, combining the 'backbone' of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs) with a 'third drug', either a PI, non-nucleoside reverse transcriptase inhibitor (NNRTI), or integrase strand transfer inhibitor (INSTI), has so far stood the test of time. The advent of the INSTIs, however, has challenged some of the established dogmas of antiretroviral therapy (ART).

Back in the day, we had to weigh up the convenience and fewer side effects of the NNRTIs with the higher resistance barrier and (perceived?) antiviral potency of the PIs when deciding on the third drug to include in the triple regimen.

Since the INSTIs have become available, particularly the more modern once-daily INSTIs that have a high barrier to resistance, clinicians have been able to offer people living with HIV (PLWHIV) a first-line 'triple therapy' that approaches the perfect combination of low pill burden, convenience of use, high intrinsic antiviral potency, high barrier to resistance development, and fewer side effects and drug-drug interactions. These INSTI-based triple therapies are particularly suited to fast-starting PLWHIV on ART, as the pre-requisite and preparation phases have shrunk to a minimum and often can be expedited in the same session of the first consultation with the antiretroviral prescriber. I can now say that all I need to start a newly diagnosed PLWHIV on treatment is for them to have stable housing; minimum income guaranteeing coverage of the pharmacy co-payment and food; and no harmful, current substance abuse.

Furthermore, recent research shows that a dual-therapy regimen combining a modern INSTI with a single NRTI well known for its innocuity (lamivudine) is a safe and effective option for PLWHIV with a prolonged previous NRTI/NtRTI exposure resulting in cardiovascular, bone, or kidney toxicity.*

The current view is, therefore, that INSTIs could become the new 'backbone' of ART, with one or two NRTIs becoming the new complement according to the stage of the infection.

* Cahn P, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019;393(10167):143-55.

Summary Table

Comparison of the advantages and disadvantages of EVG, DTG, and RAL in terms of their pharmacokinetic properties and resistance profiles and use in clinical practice.[1,2,6,17,18]

	Year of approval (US and NZ)	Advantages	Disadvantages
DTG[a]	2013 and 2014	• Once-daily dosing • Can be taken with or without food • Low propensity to cause DDIs (due to minimal metabolism by cytochrome P450) • Available as a single agent (allowing its use in other combinations) • Also registered as a fixed-dose combination tablet (allowing for simplified ART regimens with a low tablet burden) • No major contraindications • No dosage adjustment required in renal impairment • No dosage adjustment required in mild-to-moderate hepatic impairment • Low risk of resistance with virologic failure • Funded (Special Authority required)	• Small increase in serum creatinine level, which is not considered clinically relevant in the absence of a change in eGFR • Concerns about a potential increased risk of neural tube defects when DTG is used at the time of conception, although it is unclear whether this is a class effect
EVG[b]	2012 and 2013	• Once-daily dosing • Registered as a fixed-dose combination tablet (allowing for simplified ART regimens with low tablet burden) • Dosage adjustment is not required for EVG in renal impairment; however, routine kidney monitoring is required with the EVG/COBI/TDF/FTC co-formulation and renal impairment might restrict its use in some patients • No dosage adjustment of EVG or COBI required in mild-to-moderate hepatic impairment	• Should be taken with food • Requires pharmacokinetic boosting with COBI to achieve therapeutic concentrations and allow once-daily dosing • High propensity to cause DDIs (due to major cytochrome P450 metabolism and COBI boosting) • Co-formulation precludes combination with other antiretrovirals • Renal safety monitoring required if serum creatinine exceeds 0.4 mg/dL due to COBI • (inhibition of tubular secretion of creatinine) • Contraindications: concomitant use with strong Inducers of CYP3A or highly dependent CYP3A substrates • Lower barrier to resistance than DTG • Concerns about a potential increased risk of neural tube defects when DTG is used at the time of conception, although it is unclear whether this is a class effect
RAL	2007 and 2014	• Can be taken with or without food • Longest safety record of the three INSTIs • Low propensity to cause DDIs (due to minimal metabolism by cytochrome P450) • Available as a single agent, (allowing its use in other combinations) • No major contraindications • No dosage adjustments required in renal impairment • No dosage adjustment is required in mild to moderate hepatic impairment • Preferred INSTI in pregnancy in the IAS-USA treatment recommendations • Funded (Special Authority required)	• Twice-daily dosing • Not co-formulated as part of a complete regimen • Part of ART regimens with a higher pill burden relative those of the other INSTIs • Lower barrier to resistance than DTG • Concerns about a potential increased risk of neural tube defects when DTG is used at the time of conception, although it is unclear whether this is a class effect

a DTG as dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) fixed-dose combination tablet has also been registered (but not yet marketed) in NZ
b EVG as EVG/COBI/TDF/FTC fixed-dose combination tablet is registered in NZ but no yet marketed.
Abbreviations: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; COBI = cobicistat; DDI = drug-drug interaction; DTG = dolutegravir; EVG = elvitegravir; FTC = emtricitabine; eGFR = estimated glomerular filtration rate; INSTI = integrase strand transfer inhibitor; RAL = raltegravir; TDF = tenofovir disoproxil fumarate.

REFERENCES

1. Saag MS, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel. JAMA. 2018;320(4):379-96.
2. Podany AT, et al. Comparative clinical pharmacokinetics and pharmacodynamics of HIV-1 integrase strand transfer inhibitors. Clin Pharmacokinet. 2017;56(1):25-40.
3. Anonymous. Raltegravir (Isentress) Data Sheet (24 May, 2018). Auckland: Merck Sharp & Dohme (New Zealand) Limited. 2018. Available from: https://medsafe.govt.nz/profs/Datasheet/i/Isentresstab.pdf.
4. Anonymous. Dolutegravir (Tivicay) Data Sheet (14 June, 2018). Auckland: GalxoSmithKline (NZ) Ltd. 2018. Available from: https://medsafe.govt.nz/profs/Datasheet/t/tivicaytab.pdf.
5. Anonymous. Tenofovir disoproxil fumarate/emtricitabine/elvitegravir/cobicistat (Stribild) Data Sheet (19 September, 2017). Auckland: Gilead Sciences (NZ). 2017. Available from: https://medsafe.govt.nz/profs/Datasheet/s/stribildtab.pdf.
6. Anonymous. Strand transfer inhibitors. Online Pharmacetical Schedule - March 2019. Wellington: PHARMAC. Last update date: March 2019. Available from: https://www.pharmac.govt.nz/wwwtrs/ScheduleOnline.php?code=A162007. [Date accessed: 07/03/19].
7. Unger NR, et al. Elvitegravir for the treatment of HIV. Expert Opin Pharmacother. 2016;17(17):2359-70.
8. Sharma M, et al. Raltegravir as antiretroviral therapy in HIV/AIDS. Expert Opin Pharmacother. 2014;15(3):395-405.
9. McCormack PL. Dolutegravir: a review of its use in the management of HIV-1 infection in adolescents and adults. Drugs. 2014;74(11):1241-52.
10. Liedtke MD, et al. Long-term efficacy and safety of raltegravir in the management of HIV infection. Infect Drug Resist. 2014;7:73-84.
11. Kandel CE, et al. Dolutegravir - a review of the pharmacology, efficacy, and safety in the treatment of HIV. Drug Des Devel Ther. 2015;9:3547-55.
12. Deeks ED. Elvitegravir: a review of its use in adults with HIV-1 infection. Drugs. 2014;74(6):687-97.
13. Raffi F, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet. 2013;381(9868):735-43.
14. Cahn P, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet. 2013;382(9893):700-8.
15. Molina JM, et al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. Lancet Infect Dis. 2012;12(1):27-35.
16. Anonymous. Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. AIDSinfo. Bethesda, MD: National Institutes of Health (NIH). U.S. National Library of Medicine. Last update date: November 2018. Available from: https://aidsinfo.nih.gov/drugs/507/stribild/165/professional#nlm34090-1. [Date accessed: 09/01/18].
17. Wong E, et al. HIV pharmacotherapy: A review of integrase inhibitors. JAAPA. 2016;29(2):36-40.
18. Elliot E, et al. How recent findings on the pharmacokinetics and pharmacodynamics of integrase inhibitors can inform clinical use. Curr Opin Infect Dis. 2017;30(1):58-73.
19. Anonymous. Dolutegravir. AIDSinfo. Bethesda, MD: National Institutes of Health (NIH). U.S. National Library of Medicine. Last update date: September 2018. Available from: https://aidsinfo.nih.gov/drugs/509/dolutegravir/167/professional. [Date accessed: 11/01/19].
20. Anonymous. Raltegravir. AIDSinfo. Bethesda, MD: National Institutes of Health (NIH). U.S. National Library of Medicine. Last update date: March 2018. Available from: https://aidsinfo.nih.gov/drugs/420/raltegravir/13/professional. [Date accessed: 11/01/19].
21. Zash R, et al. Neural-tube defects with dolutegravir treatment from the time of conception. N Engl J Med. 2018;379(10):979-81.
22. Zash R, et al. Surveillance for neural tube defects following antiretroviral exposure from conception. 22nd International AIDS Conference; 23-27 July, 2018; Amsterdam. 2018. Available from: http://www.natap.org/2018/IAC/IAC_52.htm. [Date accessed: 15/02/19].
23. Dooley K, et al. Safety and efficacy of dolutegravir-based art in TB/HIV coinfected adults at week 24. 25th CROI (Conference on Retroviruses and Opportunistic Infections); 4-7 March, 2018; Boston, MA. 2018. Oral Abstract 33. Available from: http://www.croiconference.org/sessions/safety-and-efficacy-dolutegravir-based-art-tbhiv-coinfected-adults-week-24. [Date accessed: 08/01/19].
24. You J, et al. Therapy-emergent drug resistance to integrase strand transfer inhibitors in HIV-1 patients: A subgroup meta-analysis of clinical trials. PLoS One. 2016;11(8):e0160087.
25. Wohl DA, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. J Acquir Immune Defic Syndr. 2014;65(3):e118-20.
26. Walmsley S, et al. Brief report: Dolutegravir plus abacavir/lamivudine for the treatment of hiv-1 infection in antiretroviral therapy-naive patients: Week 96 and week 144 results from the Single randomized clinical trial. J Acquir Immune Defic Syndr. 2015;70(5):515-9.
27. Sax PE, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385(9987):2606-15.
28. Rockstroh JK, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. J Acquir Immune Defic Syndr. 2013;63(1):77-85.
29. Orrell C, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Lancet HIV. 2017;4(12):e536-e46.
30. Molina JM, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. Lancet HIV. 2015;2(4):e127-36.
31. Lennox JL, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. Ann Intern Med. 2014;161(7):461-71.
32. Clumeck N, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. J Acquir Immune Defic Syndr. 2014;65(3):e121-4.
33. Thierry E, et al. Different pathways leading to integrase inhibitors resistance. Front Microbiol. 2016;7:2165.
34. Metifiot M, et al. Resistance to integrase inhibitors. Viruses. 2010;2(7):1347-66.
35. Hare S, et al. Structural and functional analyses of the second-generation integrase strand transfer inhibitor dolutegravir (S/GSK1349572). Mol Pharmacol. 2011;80(4):565-72.
36. Hightower KE, et al. Dolutegravir (S/GSK1349572) exhibits significantly slower dissociation than raltegravir and elvitegravir from wild-type and integrase inhibitor-resistant HIV-1 integrase-DNA complexes. Antimicrob Agents Chemother. 2011;55(10):4552-9.
37. Anstett K, et al. HIV drug resistance against strand transfer integrase inhibitors. Retrovirology. 2017;14(1):36.
38. Tsiang M, et al. Antiviral activity of bictegravir (GS-9883), a novel potent HIV-1 integrase strand transfer inhibitor with an improved resistance profile. Antimicrob Agents Chemother. 2016;60(12):7086-97.
39. Di Perri G, et al. The clinical pharmacology of integrase inhibitors. Expert Rev Clin Pharmacol. 2018 Dec 4 [Epub ahead of print].

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