A RESEARCH REVIEW™ SPEAKER SERIES

Dolutegravir-based regimens:

Scientific and clinical evidence for a high barrier to resistance

Making Education Easy 2018

About the Speaker

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Jim obtained his PhD in Genetics from the George Washington University with research at the National Institutes of Health/ Allergy and Infectious Disease (NIAID) and did his post-doctoral fellowship at Duke University on the initial immune response to primary HIV infection.

Jim is currently the Director of Microbiology Strategy at ViiV Healthcare where he oversees the global strategy for the treatment of HIV infection. He is also Adjunct Assistant Professor of Immunology at Duke University School of Medicine, Durham, NC, USA.

Previously as Senior Chief Scientist at GSK he led a group of scientists working on early phase drug discovery and clinical trials of novel therapies for HIV infection as well as working on immune-based approaches for HIV and other viral diseases.

Abbreviations used in this review:

3TC = lamivudine
ABC = abacavir
ART = antiretroviral therapy
ATV = atazanavir
BR = background regimen
DRV = darunavir
DTG = dolutegravir
EFV = efavirenz
EVG = elvitegravir
FC = fold change
FTC = emtricitabine
INSTI = integrase strand transfer inhibitor
LPV = lopinavir
NNRTI = non-nucleoside reverse transcriptase inhibitor
NRTI = nucleoside reverse transcriptase inhibitor
OBR = optimised background regimen
PDVF = protocol-defined virologic failure
PI = protease inhibitor
RAL = raltegravir
RTV = ritonavir
TDF = tenofovir disoproxil fumarate

This review is a summary of a recent presentation by Dr James Demarest, Director of Microbiology Strategy at ViiV Healthcare. Dr Demarest discussed the scientific and clinical evidence for the high barrier to resistance of dolutegravir-based regimens in the treatment of HIV-1 infection. Dr Demarest's talk was presented to healthcare professionals in Auckland via video by Dr Fraser Drummond, Medical Director Australasia ViiV Healthcare.

HISTORY OF INTEGRASE STRAND TRANSFER INHIBITORS

Everyone is familiar with the advent of highly active antiretroviral therapy (HAART) in the mid 1990's that had a significant impact on HIV-related morbidity and mortality. Despite these advances, there remain certain challenges for long term treatment success.

Attributes of a drug or drug regimen in terms of pharmacokinetics, potency, resistance, toxicity and tolerability profile are important in this regard. At the patient level, challenges regarding long term adherence, tolerability/toxicities, and even social/personal issues may come to bear. At the virus level, limitations include the selection of resistant virus that is capable of replicating in the presence of drug. These all represent some of the major challenges for long term success on HAART regimens. Some drug classes have taken longer than others to come from bench to bedside. Such is the case with HIV integrase strand transfer inhibitors (INSTIs).

Integrase has long been a therapeutic target for HIV treatment. Twenty-seven years ago, researchers were able to express the HIV integrase enzyme and show that it had activity *in vitro*.[1] Ten years later, data were published demonstrating the antiviral effect of an HIV INSTI.[2] In 2007, 17 years after the *in vitro* enzyme data and 10 years post the advent of HAART, raltegravir was licensed as a twice-daily agent. Raltegravir was the first INSTI to demonstrate non-inferiority to the gold standard regimen at the time (efavirenz-based regimens).[3,4]

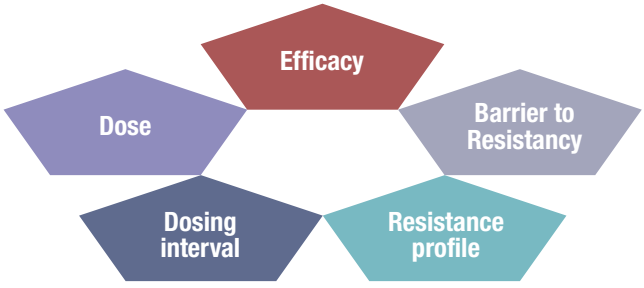
In 2013 in the EU, the second INSTI, elvitegravir, was licensed as a once-daily fixed-dose combination with a booster (cobicistat) and two nucleoside reverse transcriptase inhibitors (NRTIs). Cobicistat is required to boost the levels of elvitegravir to overcome the short half-life of the drug and to allow for once-daily dosing. Elvitegravir/cobicistat was the second INSTI to demonstrate non-inferiority to efavirenz-based regimens.[5-7]

Dolutegravir was engineered to address five key areas

Despite the availability of two INSTIs, there were a number of limitations that would be ideal to overcome. Dolutegravir was engineered to address five key areas including having good efficacy, low dose (to enable single dose with another agent or as a fixed-dose combination), once-daily dosing interval, a good resistance profile, and barrier to resistance.[8]

In terms of the dose and dosing interval, data from the SPRING-1 trial show that dolutegravir has a long plasma half-life of approximately 15 hours as well as relatively low inter-patient variation in HIV-1 patients.[9] In addition, at 24 hours post dose administration, the plasma concentration or "coverage" is 19-fold above the target protein adjusted IC_{90}. These factors support once-daily dosing without the need for a booster.[10]

Dolutegravir was engineered to address five key areas



IN VITRO CHARACTERISTICS OF MARKETED INSTIs

Mechanism of action

The chemical structure of the three INSTIs currently approved for HIV treatment are shown in Figure 1.[11] There are some commonalities across the compounds, but some differences as well. All three contain the two-metal binding pharmacophore and all bind to essential metals (Mg^{2+}) in the integrase catalytic pocket. Differences in a two-dimensional view show that dolutegravir has a more streamlined structure than raltegravir or elvitegravir. Together, the structural and associated medicinal chemistry differences impact the pharmacokinetic profile, anti-HIV activity, ability to bind to and inhibit the active site of the enzyme, and the resistance profile. For example, the streamlined design of dolutegravir confers an optimal binding affinity that may contribute to the high barrier to resistance. Furthermore, comparison of the docked orientation of dolutegravir and raltegravir show clear differences; dolutegravir has a more streamlined metal-chelating scaffold compared with raltegravir, enabling it to lie distal to residue 143.[12] The architecture of dolutegravir may contribute to its resistance to residue substitutions.[12]

Finally, dolutegravir dissociation from integrase-DNA complexes is slower compared with raltegravir and elvitegravir; dolutegravir remains bound to HIV integrase 8 times longer than raltegravir and 26 times longer than elvitegravir (Figure 2).[11] Slower dissociation of dolutegravir is related to *in vitro* antiviral activity.

Resistance profile

In vitro passage studies showed that dolutegravir has a distinct resistance profile relative to raltegravir and elvitegravir.[13-15] All substitutions observed during dolutegravir passage had low level impact on dolutegravir susceptibility (fold change [FC] IC_{50} ≤4.1).[13,15] Most single, double or triple mutations that were identified during passage with raltegravir or elvitegravir did not confer resistance to dolutegravir.[15,16] These data are consistent with dolutegravir having potential for a higher barrier to resistance.

Figure 1. Structure of integrase strand transferase inhibitors[11]

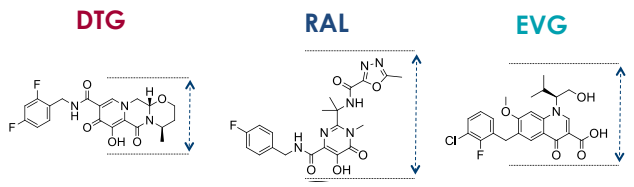
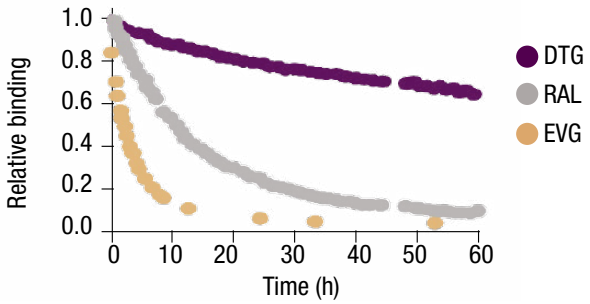


Figure 2. Dolutegravir dissociation from integrase-DNA complexes is slower than raltegravir or elvitegravir[11]



INI	k_{off} (s^{-1})	$t_{1/2}$ (h)
DTG	2.7 x 10^{-6}	71
RAL	22 x 10^{-6}	8.8
EVG	71 x 10^{-6}	2.7

K_{off} = dissociation rate

DOLUTEGRAVIR: BARRIER TO RESISTANCE IN CLINICAL TRIALS

Table 1 from the Stanford HIV Resistance Database shows the key integrase amino acid positions associated with resistance to INSTIs and the respective susceptibility based on clinical data.[17] The amino acid positions are noted across the top. The second row has the consensus amino acid. For each of the INSTIs, mutations are noted that impact susceptibility. As seen with the *in vitro* resistance passage work, dolutegravir has a different profile clinically from raltegravir or elvitegravir. Certain mutations that have a high impact on reducing susceptibility to raltegravir or elvitegravir have limited impact on dolutegravir, in particular in the absence of mutations in Q148. Mutations at 92, 138, or 140 impact raltegravir and elvitegravir more than dolutegravir. This means that resistance to dolutegravir is less likely to develop in comparison to the other two INSTIs.

The profile of dolutegravir that emerged *in vitro* has translated into clinical trial results. Dolutegravir has been studied across a wide variety of patients and demonstrated high virologic efficacy (Table 2).[18-23] In ART-naive patients dolutegravir demonstrated superiority to efavirenz[18], boosted darunavir[19] and atazanavir[23], and non-inferiority to raltegravir.[20] It showed this activity regardless of the two NRTIs used. In ART-experienced patients, dolutegravir was superior to raltegravir.[21]

Table 1. The major clinically relevant INSTI resistance mutations[17]

	66	92	138	140	143	147	148	155
Consensus	T	E	E	G	Y	S	Q	N
RAL	A	Q	KA	SA	RCH		HRK	H
EVG	IAK	Q	KA	SA		G	HRK	H
DTG		Q	KA	SA			HRK	

Orange, highest levels of reduced susceptibility or virological response to indicated INI

Blue, reduced susceptibility or virological response to the indicated INI

Red contribute to reduced susceptibility in combination with other INI resistant mutations

Table 2. Registration studies of dolutegravir in subjects with HIV[18-23]

Trial	Investigational product	Comparator	Patient population	Results
SINGLE	DTG + ABC/3TC	EFV/TDF/FTC	Treatment-naive	DTG + ABC/3TC superior to EFV/TDF/FTC
FLAMINGO	DTG (+2 NRTIs)	DRV/RTV (+2 NRTIs)	Treatment-naive	DTG superior to DRV/RTV with 2 NRTIs
SPRING-2	DTG (+2 NRTIs)	RAL (+2 NRTIs)	Treatment-naive	DTG demonstrated non-inferiority vs RAL
ARIA	DTG/ABC/3TC	ATV/RTV (+ TDF/FTC)	Treatment-naïve	DTG/ABC/3TC was superior to ATV/RTV + TDF/FTC
SAILING	DTG (+BR)	RAL (+BR)	Treatment-experienced failing current regimen	DTG superior to RAL
VIKING-3	DTG (+OBR)	N/A	INSTI-resistant	DTG effective in INST-resistant, highly treatment-experienced patient population

BR = background regimen; OBR = optimised background regimen

Treatment-naive

No treatment-emergent mutations leading to drug resistance were detected with dolutegravir in phase III trials of treatment-naïve subjects (Table 3).[10,23-27]

In SINGLE[24], 9% of dolutegravir subjects and 8% of EFV/TDF/FTC subjects had protocol-defined virologic failure (PDVF) through 144 weeks. One NRTI and six NNRTI mutations were identified in subjects treated with EFV/TDF/FTC but none were detected with dolutegravir. No INSTI mutations were detected through week 144 with either treatment arm. In the dolutegravir arm, an E157Q/P polymorphism was detected with no significant change in phenotypic susceptibility.

In FLAMINGO[25], less than 1% and 2% subjects receiving dolutegravir and DRV/RTV had PDVF at week 96. No subjects with PDVF in either arm had treatment-emergent resistance at PDVF.

In SPRING-2[10], fewer subjects had PDVF in the dolutegravir arm (5%) compared with raltegravir (7%) at week 96. None of the subjects with PDVF in the dolutegravir arm had treatment-emergent INSTI or NRTI resistance. However, three subjects receiving raltegravir + TDF/FTC and one subject receiving raltegravir + ABC/3TC had treatment-emergent resistance mutations at PDVF.[28]

In ARIA[23], 2% of subjects receiving DTG/ABC/3TC and ATV/RTV + TDF/FTC once daily had PDVF at week 48. No subjects in the DTG/ABC/3TC-treatment arm developed INSTI or ABC/3TC resistance-associated mutations. One subject in the ATV/RTV + TDF/FTC arm had a treatment-emergent NRTI-resistant mutation (M184V) at PDVF.

Characteristics of protocol-defined virologic failure

Median plasma viral load at the time of PDVF was generally similar between treatment arms in each of the dolutegravir phase III studies with treatment-naïve subjects.[28] Reportable resistance results were obtained across a range of values, including low values of <500 copies/mL (<2.7 log).

Analysing PDVF samples may offer the best chance of identifying genotypic changes, as confirmatory samples generally showed a lower plasma viral load and the time between samples varied substantially. For example, in SINGLE, the time from PDVF to the confirmatory sample ranged from 1 to 18 weeks.

Table 3. Summary of emergent mutations in dolutegravir phase III clinical trials in treatment-naïve subjects[10,23-27]

	SINGLE (to week 144)		FLAMINGO (to week 96)		SPRING-2 (to week 96)		ARIA (to week 48)	
	DTG + ABC/3TC	EFV/TDF/FTC	DTG (+2 NRTIs	DRV/r (+2 NRTIs)	DTG (+2 NRTIs)	RAL (+2 NRTIs)	DTG/ABC/3TC	ATV/r (+ TDF/FTC)
Subjects with PDVF [N (%)]	39 (9)	33 (8)	2 (<1)	4 (2)	22 (5)	29 (7)	6 (2)	4 (2)
Integrase genotypic results at baseline and time of PDVF	19	11	-	-	10	19	-	-
INSTI-resistant mutations	0	0	0	0	0	1	0	0
RT genotypic results at baseline and time of PDVF	26	16	-	-	14	20		
NRTI-resistant mutations	0	1 (K65K/R)	0	0	0	4	0	1 (M184V)
NNRTI-resistant mutations	0	6 (K101E, K103N, K103K/N, G190G/A)	-	-	-	-	-	-
PI-resistant mutations	0	0	0	0	-	-	0	0

Treatment-experienced, INSTI-naïve

In the randomised, double-blind SAILING study[21], dolutegravir 50 mg once daily, together with an optimised background regimen, exerted a greater virological effect than raltegravir 400 mg twice daily in ART-experienced, integrase-inhibitor-naïve adults with HIV-1.

Treatment-emergent INSTI resistance substitutions occurred less frequently with dolutegravir than with raltegravir: at week 48, amongst subjects with PDVF, only four (24%) developed INSTI resistance during dolutegravir treatment, compared with 16 (42%) who received raltegravir. Two dolutegravir subjects had HIV-1 with K substitutions at position R263 at the time of virologic failure, with FC in IC_{50} <2 to dolutegravir. A further two subjects had E138T/A and T97A mutations. Of note, one dolutegravir subject with emergent INSTI resistance (post 48 weeks) was non-adherent with the investigational product (protocol deviation); this likely contributed to virologic failure and emergence of resistance.[29]

Subjects receiving dolutegravir plus two NRTIs over 48 weeks did not experience PDVF (0/32), even when both NRTIs were not fully active (Table 4).[30] Seven of 32 (22%) subjects receiving raltegravir plus 1–2 NRTIs experienced PDVF. In subjects receiving protease inhibitor (PI)-containing background regimens, 18/300 (6%) of dolutegravir subjects and 36/305 (12%) of raltegravir subjects experienced PDVF. Among subjects for whom the background regimen included 3TC or FTC plus a second NRTI in the presence of mutation M184V, 0/13 in the dolutegravir group had PDVF compared with 4/12 (33%) in the raltegravir group.

Table 4. SAILING: PDVF at week 48 by type of background regimen[30]

	DTG PDVF [N (%)]	RAL PDVF [N (%)]
Overall	21/354 (6)	45/361 (12)
NRTI-only background regimens	0/32	7/32 (22)
2 fully active NRTIs	0/16	3/19
1 fully active NRTI	0/12	4/13
0 fully active NRTIs	0/1	–
Missing phenotype	0/3	–
PI-containing background regimens	18/300 (6)	36/305 (12)
Other background regimens	3/22 (14)	2/24 (8)

Treatment-experienced, switching to dolutegravir

STRIIVING was a phase III trial of 553 treatment-experienced virologically-suppressed adult subjects with HIV switched to DTG/ABC/3TC.[31] Patients had achieved and maintained virological suppression (HIV-1 RNA <50 copies/mL) on an ART regimen that had been stable for ≥6 months prior to screening. Patients were randomised to DTG/ABC/3TC on day one (early switch) or continued on current ART and switched at week 24 (late switch). The study continued to 48 weeks for both study arms.

At week 24, 85% of early switch subjects were virologically suppressed versus 88% of late switch subjects. At week 48, 83% and 92% were virologically suppressed in the early and late-switch groups, respectively. Therefore, DTG/ABC/3TC was non-inferior to current ART. No subjects (early or late switch) met PDVF (HIV RNA ≥400 copies/mL at 2 consecutive assessments any time after randomisation). At the week 48 assessment, one early switch subject and three late switch subjects had a viral load ≥50 copies/mL. However, all four subjects subsequently re-suppressed and all achieved a viral load <50 copies/mL. HIV Treatment Satisfaction Questionnaire scores improved in participants switching to ABC/DTG/3TC versus current ART.

Treatment-experienced, second line

DAWNING[32] is a non-inferiority study conducted to compare a PI-sparing regimen of dolutegravir plus 2 NRTIs with a current WHO-recommended regimen of LPV/RTV plus 2 NRTIs in HIV-1-infected subjects failing first-line therapy of an NNRTI plus 2 NRTIs. The primary endpoint is the proportion of subjects with HIV-1 RNA <50 copies/mL at week 48 using the FDA snapshot algorithm (12% non-inferiority margin).

The independent data monitoring committee (IDMC) completed two of three pre-planned analyses, and the study continued according to the study protocol. Following their second pre-planned analysis, the IDMC conducted an ad hoc review of week 24 data and large subsets of data from weeks 36 and 48. The IDMC recommended discontinuation of the LPV/RTV arm because of differences in rates of virologic nonresponse (FDA snapshot) and increasing differences in rates of PDVF favouring the dolutegravir arm. The study protocol has been amended to allow ongoing LPV/RTV subjects to switch to the dolutegravir arm.

At week 24 (ITT analysis), 82% of subjects on dolutegravir versus 69% on LPV/RTV achieved HIV-1 RNA <50 copies/mL ($p<0.001$) (Figure 3). This difference was primarily driven by higher rate of virologic failure (snapshot) in the LVP/RTV arm. Dolutegravir + 2 NRTIs had a favourable safety profile compared to LPV/RTV + 2 NRTIs.

At week 16, less than 1% of subjects in each group had confirmed virologic withdrawal criteria. At week 24 the proportions were 2% and 6%, in the dolutegravir + 2 NRTIs versus LPV/RTV + 2 NRTIs groups respectively, and at any time (up to week 52), the proportions were 3% and 9%, respectively. No subject with confirmed virologic withdrawal receiving dolutegravir + 2 NRTIs developed INSTI or NRTI resistance-associated mutations, versus three receiving LPV/RTV + 2 NRTIs (one subject developed both K70R and M184V, another developed K70R and K219E and one developed K219Q).

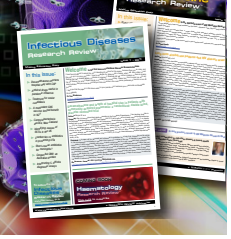
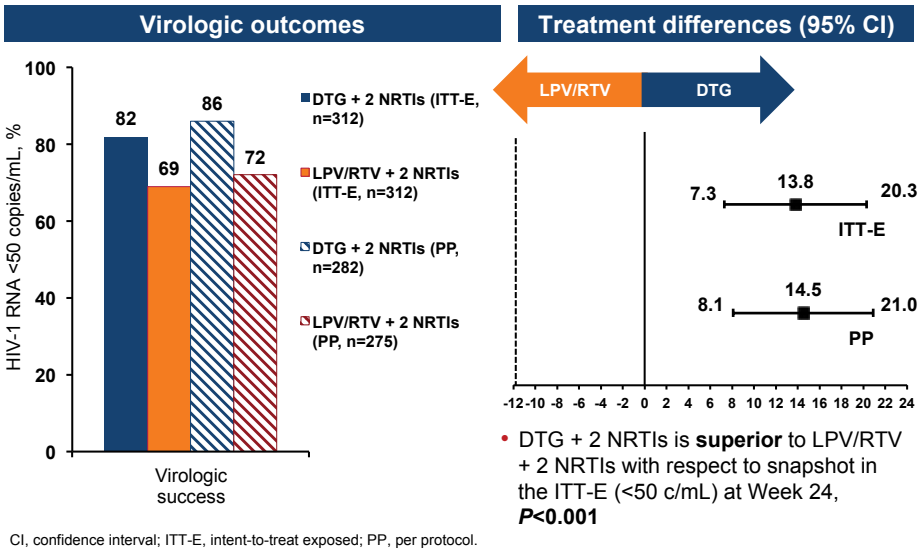


Figure 3. DAWNING: Snapshot outcomes at week 24[32]



CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

OVERALL CONCLUSIONS

Preclinical

- *In vitro* experiments support the potential for dolutegravir to have a higher barrier to resistance when compared to raltegravir and elvitegravir.[13-16]
- As yet there is no *in vivo* evidence of emergence of novel mutations that result in a substantial decrease in dolutegravir susceptibility.[33-35]
- Slow dissociation of dolutegravir, and the need for multiple raltegravir-associated mutations to impact dolutegravir dissociation, may contribute to its distinctive resistance profile and higher barrier to resistance.[11]

Treatment-naïve

- No treatment-emergent mutations leading to drug resistance have been detected with dolutegravir 50 mg once daily in any clinical trial to date in treatment-naïve subjects up to 144 weeks.[20,23-25]

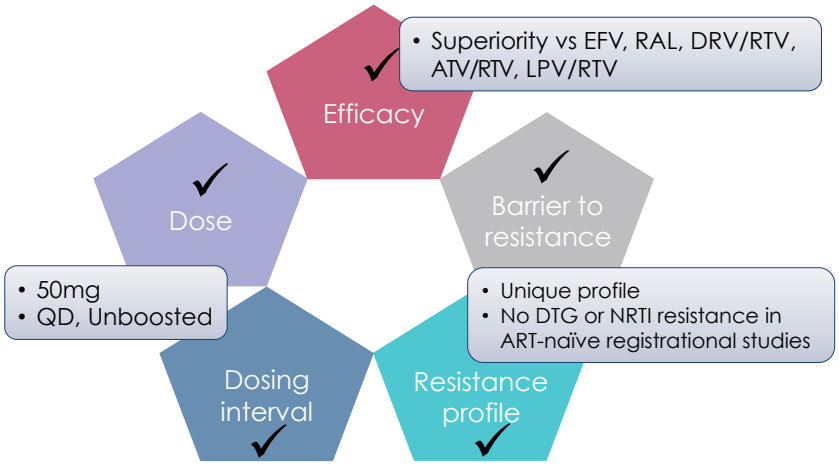
Treatment-experienced, INSTI-naïve

- In the SAILING study, lower rates of INSTI resistance to the background regimen agents were seen for the dolutegravir arm compared with the raltegravir arm.[21]

Treatment-experienced, switching to dolutegravir

- In virologically suppressed subjects (STRIIVING), no subjects switching to DTG/ABC/3TC or remaining on current therapy met the PDVF endpoint through 48 weeks.[31]

Figure 4. Dolutegravir was engineered to address five key areas[18-23,36]



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