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Genetic Barrier to Resistance for Dolutegravir

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Abstract

Dolutegravir is a novel integrase strand-transfer inhibitor that displays potent* in vitro *activity and a remarkably different resistance profile. Its robust pharmacokinetic/pharmacodynamic properties – long plasma $t_{1/2}$, high plasma inhibition quotient, and slow dissociation rate from the integrase complex – suggest it should present a high barrier to resistance development. This has been confirmed in pivotal phase III studies of initial therapy, with none out of 1,118 treated individuals selecting resistance-associated mutations at the integrase or reverse transcriptase. In integrase-naive subjects with virological failure, a rescue intervention with dolutegravir has shown significantly higher rates of virological suppression than raltegravir, as well as significantly lower rates of selection of resistance both at the integrase and against the optimized background. Unexpectedly, a mutation rarely selected in this scenario (R263K) induces a fitness cost that prevents HIV-1 from evading drug pressure, and accumulation of further secondary mutations does not occur and has not been able to compensate the replication capacity deficit in the aftermath of the appearance of a single drug resistance mutation. Therefore, both* in vitro *and* in vivo*, it leads the virus to a previously unnoticed evolutionary pathway with low chances to develop resistance to both dolutegravir and other families of antiretrovirals present in the background. This high genetic barrier to resistance development in early stages of antiretroviral treatment can help preserve future treatment options in patients who fail antiretroviral therapy. **(AIDS Rev. 2015;17:56-64)**

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Key words

Dolutegravir. Integrase inhibitor. Genetic barrier. HIV-1 resistance. Raltegravir.

Introduction

Dolutegravir (DTG), initially known as S/GSK1349572, is a novel integrase strand transfer inhibitor (INSTI) with potent *in vitro* anti-HIV activity, and an *in vitro* resistance profile remarkably different from other integrase inhibitors (raltegravir [RAL] and elvitegravir [EVG]). It can be administered once daily without pharmacokinetic boosting due to its long plasma terminal $t_{1/2}$ (15.3 hours) and favorable pharmacokinetic/pharmacodynamic properties[1].

The emergence of viral strains that are highly resistant to RAL underscored the pressing need to develop new INSTIs with improved resistance profiles[2]. Unprecedented reductions in plasma HIV-1 RNA from baseline to day 11 of up to 2.46 $\log_{10}$ copies/ml were observed in monotherapy studies with DTG at a low milligram dose[1]. In addition, a well characterized dose/response relationship was shown, with low pharmacokinetic variability, leading to the selection of 50 mg once daily (QD) for integrase-naive subjects[3].

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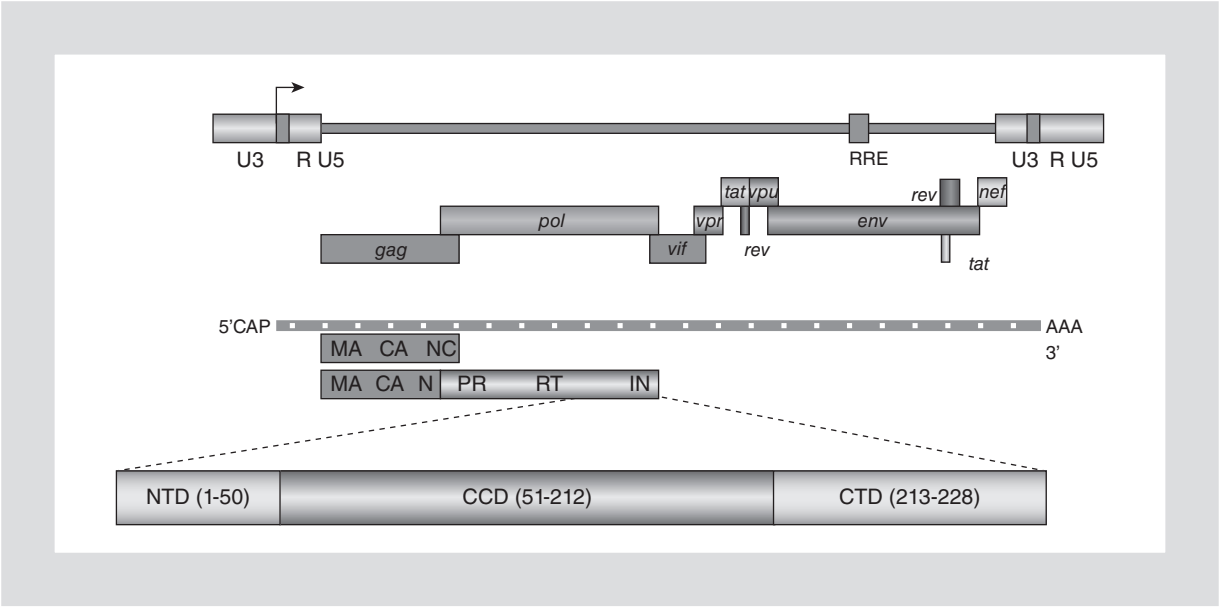


Figure 1. *General structure of HIV-1 integrase: N-terminal domain (NTD) responsible for multimerization; catalytic core domain (CCD) also binds Mg++/Mn++ and viral DNA; and C-terminal domain (CTD) binds host DNA nonspecifically.*

Unexpectedly, no subjects treated in initial therapy with DTG have so far selected any resistance-associated mutation either in the integrase or the reverse transcriptase (0/1,118 individuals at 48 weeks in pivotal randomized studies)[4-6]. In integrase-naive subjects with virological failure, salvage with DTG has shown significantly higher rates of virological suppression than RAL as well as significantly lower rates of selection of resistance[7]. Of interest, neither have these subjects selected phenotypic resistance against DTG, showing only secondary mutations that do not accumulate and are not able to achieve a significant increase in the fold-change against DTG. It maintains its activity *in vitro* against most RAL and EVG resistance strains, particularly on viruses with mutations in position 143 and 155, and has shown impressive efficacy results in salvage studies of patients with advanced failure and widespread resistance, including failure and resistance selection to previous INSTIs[8-11].

All these data, together with the finding that single initial mutations do not result in high-level resistance to DTG, suggest that it has a high genetic barrier to resistance, at least similar to that of boosted protease inhibitors (PI/r)[12]. Actually, it has a high pharmacokinetic barrier to resistance, with a C_{trough} of 1.20 µg/ml (19 times the *in vitro* protein-adjusted IC_{90} of viral suppression for wild-type virus, 0.064 µg/ml)[13]. In addition, it dissociates significantly slower from the integrase complex: 8 times longer than RAL, 26 times longer than EVG (dissociative $t_{1/2}$ 71 hours)[14].

The genetic barrier to resistance of a drug or regimen does not directly correlate with its effectiveness. For some regimens with a low genetic barrier to resistance, however, the emergence of only one or two key resistance mutations may confer complete drug resistance, not only to that drug or regimen but also to other agents, thereby limiting subsequent treatment options[15].

The present analysis reviews all the available evidence from bench to bedside, of the mechanism and clinical impact of the genetic barrier to resistance of DTG.

In vitro basics: Differences in the mechanism of action of dolutegravir

The integrase of HIV-1 (Fig. 1) catalyzes in a first step the processing of the 3' ends of the viral DNA leaving CA-reactive residues. Thereafter integrase catalyzes, in a nucleophilic attack, the insertion of the two processed ends into opposite strands of the cellular DNA in a trans-esterification reaction (strand transfer)[2]. Active integrase has a tetrameric configuration and its combination with the viral DNA (intasome) is the target of integrase inhibitors that act by inhibiting the step of strand transfer (INSTIs)[16].

Although the structure of INSTIs is diverse, all have (Fig. 2) a motif for binding and sequestration of Mg^{++}, Mn^{++}, and a hydrophobic region in the form of a halobenzolic ring that displaces the 3'- viral DNA from the cavity occupied in integrase[17]. Structural studies indicate that this displacement of the reactive

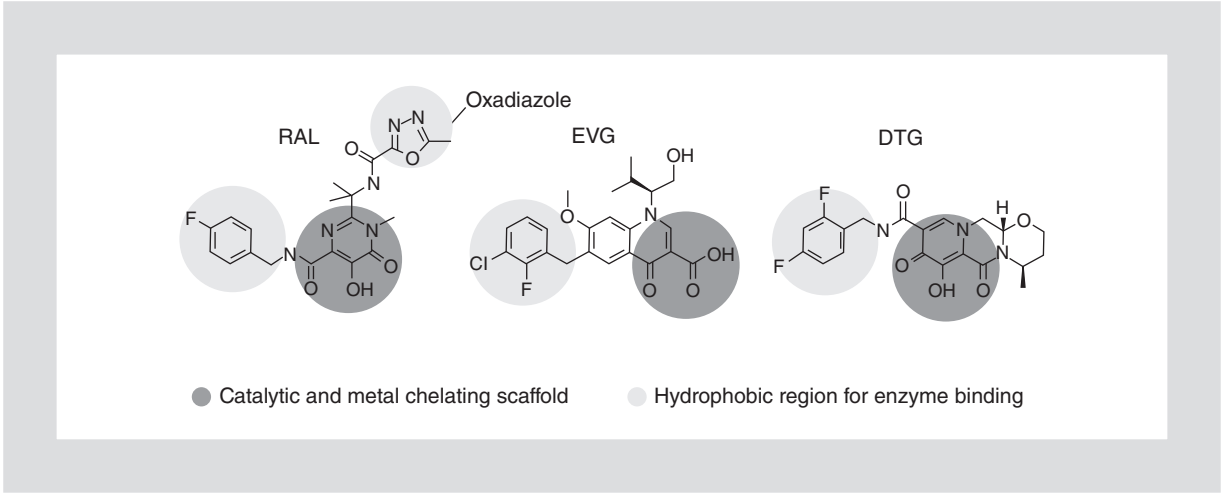


Figure 2. *Structural differences among integrase strand transfer inhibitors: dolutegravir lacks the oxadiazole group that makes raltegravir dependent on interaction with Y143. In dolutegravir the linker connecting the metal chelating group and the hydrophobic group allows a deeper and more stable position into the pocket vacated by the displaced 3' end viral DNA. DTG: dolutegravir; EVG: elvitegravir; RAL: raltegravir.*

3 'end of the viral DNA from the active site is primarily responsible for the activity of INSTIs, which is the real Achilles heel of integration[17,18]. Additionally, INSTIs mediate the sequestration of metal cofactors Mg^{++}, Mn^{++} required for enzyme activity and secondarily interfere sterically with the binding of cellular DNA by the intasome[16].

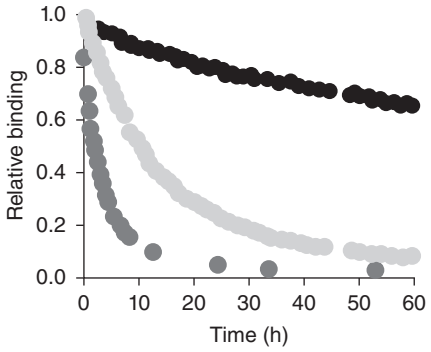
Dolutegravir exhibits structural differences with other INSTIs (RAL, EVG) that explain its antiviral potency and high genetic barrier (Fig. 2): (i) the halobenzolic ring penetrates deeper into the cavity occupied in integrase by the 3 'end of viral DNA adopting a more stable configuration, (ii) streamlined architecture of its metal-chelating scaffold within integrase, (iii) DTG lacks the oxadiazol ring which conditions dependency (π-stacking) of Y143 (RAL), and (iv) DTG undergoes subtle readjustment in position and conformation in response to structural changes in the active site of integrase with resistance mutations. All these factors contribute to a high stability of DTG in the pharmacophore and shows very low dissociation constant (K_{off}) (dissociative $t_{1/2}$ 71 hours, dissociation 8 times and 26 times slower than RAL and EVG, respectively), which likely contribute to its activity and reduce the possibility of emergence of resistance mutation (Fig. 3)[14,17,19].

In naive patients initiating treatment with DTG no integrase-associated resistance mutations have been described in virologic failure so far[4-6,20]. In experiments of *in vitro* selection of resistance with DTG, the R263K mutation has been mainly found; R263K confers low resistance to DTG but significantly reduces viral infectivity[7,9,21]. Additionally, secondary mutations (H51Y, E138K) that appear as *in vitro* selection maintained in passage experiments contribute only partially to DTG resistance and, perhaps most importantly, do not compensate for the loss of fitness induced by R263K[22]. Therefore, viral fitness cost prevents HIV-1 from evading DTG drug pressure. This combination of factors appears to be a special pathway of resistance selection in which the emergence of R263K, due to its effect fitness, leads the virus to an evolutionary pathway with low chances to develop high resistance to DTG and other families of antiretrovirals[23,24].

Resistance to integrase strand transfer inhibitors: *In vitro* data, transmitted resistance, and resistance selected at failure

Resistance to INSTIs is driven by three distinct, but not exclusive, genetic pathways, including a major (signature) mutation (Y143R/H/C, Q148H/K/R, N155H) and, very often, a minor (secondary) mutation (T66I/A/K; L74M; E92QG; T97A; E138A/K; G140S/A; S147G)[25]. These pathways have been derived from the information drawn from patients failing RAL. The Y143 pathway is less prevalent. E92Q has also been considered as a major mutation as it has an important impact (> 20 fold) on EVG resistance[26].

Both RAL and EVG show, in general, very similar resistance patterns and a high degree of cross-resistance[25]. Patients failing a RAL regimen with continuous drug pressure tend to accumulate and/or change the pattern



INI	K_{off} (S^{-1})	$t_{1/2}$ (h)
DTG	2.7×10^{-6}	71
RAL	22×10^{-6}	8.8
EVG	71×10^{-6}	2.7

Figure 3. *Integrase strand transfer inhibitor dissociation from wild-type integrase-DNA complex at 37 °C: Dissociation curves of dolutegravir, raltegravir and elvitegravir from wild-type integrase strand transfer inhibitor (left) and constants and times of dissociation (right). Both raltegravir and elvitegravir dissociated more quickly than dolutegravir with K_{off} values of 22 x 10^{-6} s^{-1} for raltegravir and 71 x 10^{-6} s^{-1} for elvitegravir. Slow dissociation occurs as the molecular architecture of integrase strand transfer inhibitor-DNA complex is resistant to substitutions due to stronger co-ordination bonds holding the complex together. This may lead to improvements in efficacy, or reduced probability of resistance emergence* (adapted from Hightower, et al.[14]). *DTG: dolutegravir; EVG: elvitegravir; INI: integrase inhibitor; RAL: raltegravir.*

of mutations. After an early appearance of N155H, an evolution to the Q148 pathway and an accumulation of further secondary mutations has been observed, mainly at codon G140[27].

Dolutegravir is a high genetic barrier INSTI, with very little cross resistance with first-generation INSTIs. Patients failing a DTG-containing first line regimen have never shown any resistance mutation[4-6,20]. The evolution of integrase mutations in antiretroviral-experienced patients failing a DTG regimen is also very low, both in INSTI-naive but antiretroviral-experienced subjects, and INSTI-experienced patients[7,10,11,28].

Transmitted drug resistance in the integrase is a rare event. Several studies have observed no transmission of major mutations, and very low rates (< 5%) of certain secondary mutations[29-33]. Genotypic testing in the integrase in naive patients prior to initial therapy is not recommended as a part of routine clinical care. The DHHS guidelines consider testing the integrase in naives only under high suspicion of integrase mutation transmission (i.e. multidrug resistance in reverse transcriptase and protease)[34].

Several studies have evaluated the prevalence of integrase mutations in patients failing a first generation integrase-containing regimen (Table 1)[2,35-40]. Prevalence rates differ from 22 to 78%, probably reflecting differences in study periods, patient characteristics, and methods used. The good news is that the Q148 pathway is less frequent (3-19%), making DTG an excellent option for salvaging first-generation integrase failures. Genotypic testing for integrase resistance in integrase-failing patients is strongly recommended by clinical guidelines.

The influence of the different HIV-1 subtypes on transmitted integrase resistance is not completely understood. Polymorphisms at positions which may influence the genetic barrier and/or drive the selection of specific integrase inhibitor resistance pathways are common, especially in HIV non-B subtypes[33].

Very few studies have addressed the role of integrase minor variants, below 20% of the viral population, either in transmitted drug resistance studies or after integrase failures. No conclusions can hence be made on this aspect so far. However, using allele-specific real-time PCR (AS-PCR) systems, Q148R variants were frequently detected, always at low level (median 0.4% of the viral population), in antiretroviral-experienced and naive patients, all them naive to integrase. Their presence was not consistently associated with virological failure, but their impact on long-term viral suppression needs to be further investigated. No minority variants exhibiting Q148H or N155H mutation were found[41]. Other studies have also rarely found secondary mutations, such as T97A and G140S, and the novel mutation E92G as minority quasispecies[32]. Actually, a novel all-inclusive HIV-1 genotypic and coreceptor tropism assay, based on deep sequencing of the protease, reverse transcriptase, integrase, and V3 regions, permits simultaneous multiplex detection of

Table 1. Main studies addressing failures to first-generation strand-transfer integrase inhibitors

	Country	n	Period	Resistance n (%)	Q148 n (%)	N155H n (%)
Alvarez, et al.[35]	Spain	77	2008-2013	17 (22.1)	2 (2.6)	10 (12.9)
Anta, et al.[36]	Spain	67	2008-2012	27 (40.3)	8 (11.9)	16 (23.9)
Delgado, et al.[40]	Spain	47	2011-2013	19 (40.4)	9 (19.1)	7 (14.9)
Santos, et al.[37]	Spain	33	2005-2013	26 (78.8)	5 (15.2)	12 (36.4)
Santoro, et al.[38]	Italy	129	2008-2013	42 (32.6)	17 (10.1)	23 (13.6)
Hurt, et al.[39]	USA	3,012	2009-2012	471 (15.7)	197 (6.6)	197 (6.6)
Garrido, et al.[65]	Spain	89	2009	30 (33.7)	8 (9.0)	15 (16.9)

low-level drug-resistant and/or non-R5 viruses, and might aid in the treatment and management of HIV-infected individuals in the near future[42].

Resistance in patients treated with dolutegravir as first antiretroviral therapy

One phase II and three bigger phase III trials have studied the efficacy of DTG plus two nucleos(t)ides (NRTI) as a first antiretroviral therapy.

In the SPRING-1 trial, 155 naive patients were treated with DTG at three different doses (10, 25, or 50 mg QD) with tenofovir/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC). After 96 weeks of follow-up no patient has developed mutations of resistance in the integrase gene, and only one developed resistance to NRTIs (M184V in one patient receiving the lower dose of DTG, 10 mg QD)[3].

A total of 411 patients received DTG (50 mg QD) for 96 weeks with TDF/FTC or ABC/3TC in the phase III SPRING-2 trial[6]. No patient developed any mutation associated with resistance to integrase inhibitors or NRTIs at the end of follow-up. The same finding was described in the SINGLE trial (414 patients receiving DTG 50 mg QD plus ABC/3TC for 144 weeks) and in the FLAMINGO trial (242 patients treated with DTG 50 mg QD plus TDF/FTC or ABC/3TC for 48 weeks)[4,5,43].

Taken together, these data show no single patient developing resistance to DTG or the accompanying NRTIs out of 1,118 patients taking DTG 50 mg QD for 48 weeks (876 patients for 96 weeks) as their first antiretroviral regimen.

This finding has no precedent in clinical trials with other recommended first-line combinations (Fig. 4).

Resistance to PI/r is not usual when these kinds of drugs are used in naive patients (0/1,348 naive patients receiving darunavir/ritonavir [DRV/r] and 2/2,280 patients treated with atazanavir/ritonavir [ATV/r] for 96 weeks in clinical trials)[44-49]. However, some few patients developed resistance to NRTIs while taking a PI/r (5/1,348 with DRV/r, and 31/2,280 with ATV/r).

Differences seem even more evident when drugs with a lower genetic barrier are utilized as first-line therapy. One hundred and thirteen patients out of 3,106 receiving efavirenz plus TDF/FTC or ABC/3TC for 96 weeks developed resistance to efavirenz, and 49 patients to NRTIs[3,4,48,50-53]. In addition, 66/1,080 naive patients who received rilpivirine plus TDF/FTC developed resistance to rilpivirine and 68/1,080 developed resistance to NRTIs[52,53].

Other first-line integrase inhibitors have also shown a different performance regarding selection of resistance after 96 weeks: 16/1,295 patients with resistance to RAL and 26/1,295 to NRTIs while receiving RAL[6,46,51]. Moreover, 14/701 selected resistance to EVG and 15/701 resistance to NRTIs while taking a regimen with EVG/cobicistat[49,50].

Some considerations must be made, however, when interpreting all this information. The incidence of virologic failure is very low with any of these recommended first-line regimens, and genotyping is not always possible during virologic failure, mainly due to technical reasons (low plasma viral load). Moreover, some differences between trials could alter the incidence of failure and resistance found in the analysis. These dissimilarities include different proportions of patients with advanced stage at baseline (higher viral load or lower baseline $CD4^+$ cell counts), different definitions for virologic failure, or different procedures to collect samples for genotyping, such as the limit of viral load or the requirement to confirm the failure before testing.

In any case, the absence of resistance described in all the trials of naive patients treated with DTG is an

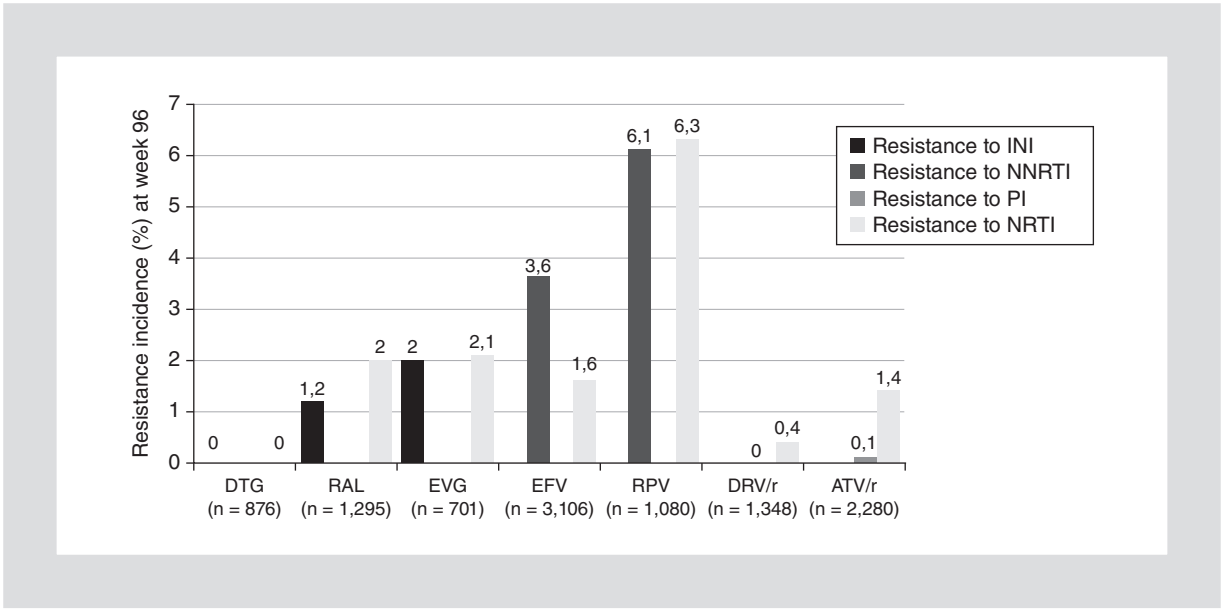


Figure 4. *Incidence of resistance at week 96 in pivotal clinical trials of antiretroviral therapy in naive patients (see text for explanation and references). INI: integrase inhibitors; DTG: dolutegravir; RAL: raltegravir; EVG: elvitegravir; NNRTI: nonnucleoside reverse transcriptase inhibitors; EFV: efavirenz; RPV: rilpivirine; PI: protease inhibitors; DRV/r: darunavir/ritonavir; ATV/r: atazanavir/ritonavir.*

interesting finding, warranting confirmation in patients treated in the real-life setting. If confirmed, the clinical implications could be very important.

Resistance in pretreated patients naive to integrase strand transfer inhibitors

Dolutegravir has also been challenged in treatment-experienced patients with virological failure in an early stage of antiretroviral treatment failure and HIV-1 resistance, with only an "intermediate" resistance scenario in integrase-naive patients (SAILING study). It confirmed its strength in a head-to-head comparison with RAL[7]. In this particular scenario of "intermediate" resistance and integrase-naive patients, the 145 study had previously shown that RAL and EVG had the same behavior in efficacy, virological failure, and resistance mutation selection at failure[54,55]. Elvitegravir has a predilection for selecting resistance mutations at codon 92 vs. 155 in the case of RAL, despite both codons having a joint trend. In addition, the study found a similar proportion of patients selecting viruses with 148 mutations, which is more difficult to rescue with DTG, with only minor differences among both INSTIs: RAL preferably replaces the wild-type amino acid for histidine and EVG for arginine.

Focusing on the SAILING study[7], data are truly impressive under all items and resemble for its similarity the TITAN study with DRV/r vs. LPV/r[56,57]. SAILING is a randomized, double-blind study with an active-controlled design that would mitigate the advantage of once-daily dosing of DTG (50 mg QD in this early scenario) vs. the twice daily administration of RAL. Dolutegravir was significantly more effective globally at week 48, meeting superiority, but was also clearly better in difficult-to-treat patients, like those with HIV-1 plasma viremia > 50,000 copies/ml and those with prior use of DRV or use of DRV with primary protease mutations. Finally, DTG had a much lower failure rate and significantly lower rates of resistance selection (predefined endpoint), both genotypic or phenotypic, against both the integrase and the backbone NRTIs. Only four (1%) patients in the DTG arm versus 17 (5%) in the RAL group selected resistance (adjusted difference –3.7% [–6.1%, –1.2%])[7].

The meticulous analysis of resistance mutations in the SAILING study reveals that RAL-treated subjects selected primary and secondary integrase mutations, which has already been described in other studies[51]. Meanwhile, in the DTG group only four out of 354 patients selected any integrase mutation. One of them should have been excluded because the patient had primary resistance (Q148H/G140S pathway) at baseline that conferred complete DTG and RAL resistance, and added at failure E138T/A and T97A mutations. Two patients developed the R263K mutation and one patient developed the polymorphic integrase substitution V151I. None of the mutations in these three patients

involved a significant increase in phenotypic resistance against DTG. The R263K mutation may be the key in explaining how difficult it is to accumulate resistance in DTG failures because it produces an important deterioration of fitness that poses for viral quasispecies a great difficulty for replicating and probably infecting. The accumulation of further secondary integrase mutations, which hypothetically should restore viral replication, does not succeed in repairing the replication deficit. Actually, the presence of resistance mutations against DTG (mainly R263K, but also G118R and/or H51Y) also impair the emergence of resistance against reverse transcriptase inhibitors (both NNRTI and NRTIs) during *in vitro* selection experiments[23]. Therefore, it could even have potential clinical benefits if confirmed[24]. Therefore, DTG displays a differentiated response in integrase-naive patients with virological failure versus RAL.

Data in patients with prior virological failure with integrase strand transfer inhibitors

First-generation integrase inhibitors, RAL and EVG, have been shown to be highly effective for the treatment of antiretroviral- naive patients. These first-generation integrase inhibitors have only a modest genetic barrier to resistance and largely share common resistance pathways, and therefore there is broad cross-resistance between RAL and EVG[2,58]. Dolutegravir has shown to retain *in vitro* activity against clinical isolates obtained from subjects who failed first-generation INSTI-based therapy[59], and potency against all integrase-resistant single mutants selected by RAL and EVG after virological failure. Viruses containing double or more mutants including Q148X are associated with diminished responses to DTG-containing regimens[59-62]. Three clinical trials have evaluated the activity of DTG in heavily pretreated patients harboring RAL- and/or EVG-resistant virus.

Viking is a phase IIb study that, in a sequential cohort design, explored two different doses of DTG (50 mg once daily or 50 mg twice daily) in 51 HIV-1-infected subjects with genotypic resistance to RAL: cohort I: 50 mg QD (n = 27) vs. cohort II: 50 mg BID (n = 24)[28]. Even though its sequential design and the fact that both cohorts had some differences in baseline characteristics, this was the first study showing that DTG 50 mg twice daily with an optimized background therapy provided greater and more durable benefit than the once-daily regimen in subjects with HIV-1 resistant to RAL.

Viking-3 was the phase III study that assessed the dose of DTG 50 mg BID, chosen after the phase IIb study, in 183 patients[11]. These patients had to have resistance to multiple antiretrovirals including integrase inhibitors. After seven days of functional monotherapy with DTG, patients optimized their background regimen with at least one fully active drug and continued with DTG as well. In this study, DTG showed a potent intrinsic antiviral activity with a seven day viral load decay of –1.43 $\log_{10}$ c/ml. After optimizing the patients' background, 69 and 63% of patients achieved virological suppression (viral load < 50 copies/ml) at week 24 and 48 of treatment, respectively. Baseline resistance to INSTIs (particularly the presence of Q148X + ≥ 2 resistance-associated mutations) and baseline viral load, but not pre-dose DTG concentrations, were significant predictors of the week 24 response[61].

Viking-4 is a multicenter study with an initial seven day, placebo-controlled randomized phase. This study was obliged by the Food and Drug US Administration (FDA) to exclude a potential antiviral effect of the current failing regimen. At baseline, subjects were randomized to receive DTG 50 mg BID or placebo plus the remaining components of the failing regimen[10]. At day 8, all subjects from both arms entered an open-label phase and received open-label DTG 50 mg BID with an optimized background regimen containing at least one fully active drug. Thirty subjects were randomized (1:1) to receive either DTG 50 mg BID or placebo. The mean change from baseline viral load at day 8 was –1.06 HIV-1 RNA ($\log_{10}$ copies/ml) vs. +0.10 in the DTG and placebo arms, respectively. At day 8, the drop in viral load was –1.43 in the group of "no Q148X mutation" (n = 5), –0.87 in the group of "Q148X+1 resistance-associated mutations G140A/C/S, L74I or E138A/K/T" (n = 6), and –0.90 in the "Q148X+2 resistance-associated mutations".

A novel mutational pathway involving integrase mutations A49P and L234V, leading to DTG resistance, has been recently reported in a highly treatment-experienced subject with the N155H RAL mutation, in the absence of Q148X mutations[63]. It conferred 63.6-fold resistance to DTG and a maximum of 150-fold cross-resistance to RAL and EVG susceptibility, with significant declines in viral replicative capacity (41%).

Therefore, the study has confirmed the activity of DTG in advanced virological failures with widespread resistance, including failure to and resistance selection against INSTIs, with diminished activity in subjects harboring Q148X-associated patterns of mutations. The

frequency of selection of DTG resistance in subjects failing a RAL-containing salvage regimen is not low. In some studies it has been shown to approach 35% of subjects, in most cases with the combination of Q148H/R/K with G140S/A mutations[64]. Hence, patients failing first-line INSTIs must rapidly change their regimen to avoid the evolution of resistance under continued drug pressure.

Conclusion

Dolutegravir exhibits a high genetic barrier to resistance that prevents resistance selection in initial therapy, both in the integrase and in the reverse transcriptase. No patients so far treated in pivotal phase III studies on initial therapy have developed resistance-associated mutations at 48 or 96 weeks. In integrase-naive patients with virological failure, no phenotypic resistance against DTG has either been selected. Surprisingly, the rare selection of some secondary mutations (R263K, G118R and/or H51Y) in this scenario are unable to compensate the fitness deficit, and could also impair *in vitro* the emergence of resistance against reverse transcriptase inhibitors (both NNRTI and NRTIs). The high pharmacokinetic barrier and some selected pharmacodynamic properties (affinity and dissociation time from the intasome) explain this barrier to resistance, unprecedented not only among INSTIs but also among the rest of antiretrovirals, that can help preserve future treatment options in patients who fail antiretroviral therapy.

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Contributors

All authors contributed with their part of the review analysis. JML wrote the first draft of this manuscript. All authors reviewed and amended the draft report.

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