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REVIEW ARTICLE

Integrase strand transfer inhibitors in the management of HIV-positive individuals

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The use of highly active antiretroviral therapy against human immunodeficiency virus (HIV) can lead to rare instances of treatment failure and the emergence of drug resistance. HIV drug-resistant strains are archived in cellular reservoirs, and this can exclude the future efficacy of drugs or drug classes against which resistance has emerged. In addition, drug-resistant viruses can be transmitted between individuals. HIV drug resistance has been countered through the constant development of new antiretroviral drugs. Integrase strand transfer inhibitors, that actively block the integration of the HIV genome into the host DNA, represent the most recent antiretroviral drugs. Of these, raltegravir, elvitegravir, and dolutegravir are the only integrase strand transfer inhibitors that have been approved for human therapy by the US Food and Drug Administration. Dolutegravir is unique in its ability to seemingly evade HIV drug resistance in treatment-naïve individuals. Here, we review the use of integrase strand transfer inhibitors in the management of HIV, focusing on HIV resistance.

Key words: Dolutegravir, drug resistance, elvitegravir, integrase strand transfer inhibitors, HIV, raltegravir

Key messages

- Integrase strand transfer inhibitors (INSTIs) can be used both as first- and second-line drugs and can outperform INSTI-sparing regimens.
- Dolutegravir is the only antiretroviral drug not yet associated with *de novo* emergence of resistance mutations in treatment-naïve individuals.

Introduction

In high-income countries, HIV infection is treated with a combination of drugs, typically two nucleos(t)ide reverse-transcriptase inhibitors (NRTI) and a ritonavir-boosted protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (1). The efficacy of this highly active antiretroviral therapy (HAART) relies on the combination of several drugs that together limit the emergence of HIV drug resistance, as has been observed to emerge quickly in monotherapy (2). HIV drug-resistant strains can be archived into the host genome of long-lived reservoir cells and can be transmitted between individuals (2). Since the potency of HAART depends on the combination of active compounds, resistance to one drug or one drug class can facilitate the emergence of resistance against the other drugs and lead to the development of multi-drug-resistant (MDR) strains. To limit HIV drug resistance, it is important to ensure that individuals living with HIV have access to efficacious antiretroviral drugs with few adverse effects and simplified dosing. Improving compliance helps to reduce the development of drug resistance and can reduce HIV transmission rates.

Integrase strand transfer inhibitors (INSTIs) are the newest antiretroviral (ARV) drug class and include raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG). The HIV integrase enzyme catalyses the irreversible integration of HIV reverse transcribed viral DNA into the host genome through two successive reactions called 3' processing and strand transfer (3). To date, all integrase inhibitors approved for therapy specifically target the second step of the integration process (4,5) through Pi-stacking with the long terminal repeats that are located at both extremities of reverse transcribed HIV DNA molecules and through coordinating Mg^{2+} ions that are necessary for integration. INSTIs are safe and efficacious for individuals living with various HIV subtypes (6–13). We review here the use of INSTIs in the management of HIV-positive individuals and compare RAL, EVG, and DTG in regard to their efficacy and resistance profiles.

Integrase inhibitors for first-line treatment

Treatment-naïve patients can benefit from INSTIs, as demonstrated by numerous clinical trials (Table I). The QDMRK study has shown that RAL should be administered twice rather than once a day (14). The STARTMRK clinical trial showed that 86.1% and 81.9% of treatment-naïve individuals receiving RAL twice daily

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Table I. Clinical trials of INSTIs versus other drug classes in first-line treatment (ARV-naïve patients).

Study	Regimen	Patients, *n*	Weeks of treatment	% With pretreatment viral load > 100,000 copies/mL	Median CD4 cell count at baseline (cells/mm^3)	HIV-RNA < 50 copies/mL	% Adverse events related to drug
STARTMRK:							
1) Rockstroh, DeJesus. JAIDS 2013	RAL + TDF/FTC vs EFV + TDF/FTC	281 vs 282	48	55.8 vs 51.8	218 vs 212	86.1 vs 81.9	44.1 vs 77
2) Lennox, DeJesus. JAIDS 2010			96			81 vs 79	47 vs 78
3) Lennox, DeJesus. Lancet 2009			240			71 vs 61.3	52 vs 80.1
Protocol 004:							
1) Markowitz, Nguyen. JAIDS 2009	RAL[d] + TDF/3TC vs EFV + TDF/3TC	160 vs 38	48	34 vs 34	271–338 (range)	85.6 vs 86.8	47.5 vs 71.1
2) Markowitz, Nguyen. JAIDS 2007			96			83.1 vs 84.2	51.3 vs 73.7
GS-US-236-0102 study:							
1) Sax, DeJesus. Lancet 2012 2) Zolopa, Sax. JAIDS 2013	EVG/C + TDF/FTC vs EFV + TDF/FTC	348 vs 352	48	34 vs 33	376 vs 383	87.6 vs 84.1	4 vs 5[a]
GS-236-0103:							
1) DeJesus, Rockstroh. Lancet 2012	EVG/c + TDF/FTC vs ATV/r + TDF/FTC	353 vs 355	48	42 vs 40	351 vs 366	89.5 vs 86.8	9.6 vs 14.1
2) Rockstroh, DeJesus. JAIDS 2013			96			83 vs 82	
SPRING-1:							
1) VanLunzen, Maggiolo. Lancet ID 2012	DTG vs EFV	205 (155 vs 50)	96	21 vs 22	Data not available	88 vs 72	14 vs 14
2) Stellbrink, Reynes. AIDS 2013	OBT: ABC/3TC or TDF/FTC						
SINGLE:							
Walmsley, Antela. NEJM 2013	DTG + ABC/3TC vs EFV + TDF/FTC	422 vs 422	48	32 vs 31	335 vs 339	88 vs 81	2 vs 10[b]
FLAMINGO:	DTG vs DRV/r						
Feinberg, Clotet. ICAAC 2013	OBT: ABC/3TC or TDF/FTC	484	48	25 vs 25	Data not available	90 vs 83	10 vs 12[c]

[a]Percentage refers to patients who discontinued a study drug because of any treatment-emergent adverse event.
[b]Percentage refers to adverse events leading to withdrawal.
[c]The most frequent side effects were diarrhoea (17% vs 29%), nausea (16% vs 18%), and headache (15% vs 10%).
[d]This was a dose-ranging study for RAL through 48 weeks. RAL was dosed at 10, 200, 400, or 600 mg BID. From week 48 to week 96, the dose used was 400 mg BID. The data in the table at 48 weeks refer to the 400 mg BID dose.
3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; BID = twice daily; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; OBT = optimized background therapy; RAL = raltegravir; TDF = tenofovir;/c = cobicistat-boosted; /r = ritonavir-boosted.

(BID) and efavirenz (EFV), respectively, along with optimized background therapy reached a plasma viral load that was < 50 copies/mL (15). Similar results were obtained after 96 weeks, with 81% versus 79% success, respectively, for RAL and EFV (16). After 5 years, 71% and 61.3% of patients attained virological suppression (17). In addition to demonstrating that RAL is non-inferior to EFV, these studies also showed that RAL caused significantly fewer adverse events than did EFV after 48 and 96 weeks of treatment (15,16). Similar observations in regard to adverse events have been made during the dose-ranging Protocol 004 clinical trials after 96 weeks (18). In these studies, RAL was also non-inferior to EFV in attainment of viral loads < 50 copies/mL after 48 and 96 weeks, when either drug was prescribed in combination with tenofovir (TDF) and lamivudine (3TC) (18,19).

Similarly to RAL, both EVG and DTG have performed extremely well during clinical trials. When co-formulated with TDF and emtricitabine (FTC), cobicistat-boosted EVG (EVG/c) was non-inferior to EFV/TDF/FTC with 87.6% and 84.1%, respectively, of treatment-naïve patients reaching a plasma viral load lower than 50 copies/mL at week 48 (20). Similar virological success was confirmed after 96 weeks of treatment (21). Notably, no differences were observed in the number of adverse events between arms (21). In addition, co-formulated EVG/c/TDF/FTC was non-inferior to ritonavir-boosted atazanavir ATV/r combined with TDF/FTC in treatment-naïve individuals at weeks 48 and 96 (22,23). Rates of patients with viral load below 50 copies/mL were 89.5% and 83%, respectively, at weeks 48 and 96 for the EVG arm versus 86.8% and 82% for the ATV/r arm (22,23).

The newest INSTI, DTG, has also demonstrated non-inferiority to EFV in the dose-ranging SPRING-1 clinical trial that employed three doses of DTG (10, 25, or 50 mg daily) and the use of either TDF/FTC or abacavir (ABC)/3TC as nucleoside backbones (24,25). At week 96, 79% to 88% of individuals receiving 10 to 50 mg DTG daily had a viral load < 50 copies/mL compared to 72% for EFV (25). More recently, in the SINGLE study, the DTG/ABC/3TC combination demonstrated superiority to EFV/TDF/FTC after 48 weeks with 88% and 81% virological success, respectively (26). In addition, DTG also demonstrated a more favourable safety and tolerability profile compared to EFV/TDF/FTC (26). The FLAMINGO study demonstrated that DTG was superior to ritonavir-boosted darunavir (DRV/r) in treatment-naïve patients (27). As detailed in the section below entitled 'Comparing integrase inhibitors', DTG when used once daily (QD) has also shown non-inferiority to RAL employed BID (28,29). Accordingly, the US Department of Health and Human Services now recommend the use of each of RAL-, EVG-, and DTG-containing regimens

for the treatment of treatment-naïve adults and adolescents living with HIV (30).

Integrase inhibitors for second-line therapy

The SECOND-LINE study demonstrated that 48 weeks of therapy with RAL in combination with ritonavir-boosted lopinavir (LPV/r) was non-inferior to r/LPV in combination with two or three NRTIs in reducing plasma viral load below 200 copies/mL (Table II). In this study, 83% and 81% of individuals who had failed previous treatment achieved virological success (31). Importantly, the EARNEST (Europe-Africa Research Network for Evaluation of Second-line Therapy) study has also tested RAL in combination with boosted PIs (99% LPV/r) as a second-line option in resource-limited settings

Table II. Clinical trials with INSTIs used in second-line treatment (ARV-experienced patients).

Study	Regimen	Patients, *n*	Weeks of treatment	% With baseline viral load > 100,000 copies/mL	Median CD4 cell count at baseline (cells/mm^3)	HIV RNA < 50 copies/mL	% Adverse events related to drug (moderate and severe)
BENCHMRK 1–2:							
1) Steigbigel, Cooper. Clin Infect Dis 2010	RAL + OBT vs placebo + OBT	466 vs 237	48	36 vs 34	119 vs 123	62.1 vs 32.9	58.4 vs 58.6 (the most common being gastrointestinal and headache)
2) Eron, Cooper. Lancet ID 2013			96			57 vs 26	
			156			51 vs 22	
SECOND-LINE: Boyd, Kumarasamy. Lancet 2013	RAL + LPV/r vs 2 or 3 NRTIs + LPV/r	270 vs 271	48	19.6 vs 20.3	190 vs 189	83 vs 81[a]	8.9 vs 8.5 (the most common being gastrointestinal)
Viking 1 − 2 (ARV-experienced and RAL-resistant patients): Eron, Clotet. J Infectious Diseases 2013	Viking 1: DTG QD + failing background therapy (RAL discontinued) for 10 days and then DTG + OBT Viking 2: DTG BID + failing background therapy (RAL discontinued) for 10 days and then DTG + OBT	27 vs 24 (Viking 1 vs Viking 2)	24	Data not available	114 vs 202	41 vs 75	No severe AEs related to DTG
Viking 3: Nichols, Lazzarin, IAS 2013. Poster TULBPE19.	DTG BID + failing background therapy (RAL and EVG discontinued) for 8 days, then DTG + OBT	184	24	Data not available	Data not available	69	Data not available
SAILING (ARV-experienced but INSTI-naïve patients): Cahn, Pozniak. Lancet 2013	DTG + OBT vs RAL + OBT	354 vs 361	48	Data not available	204 vs 193	71 vs 64	1 vs 1 (the most commonly reported AEs for DTG vs RAL were diarrhoea, upper respiratory tract infections, and headache)
EARNEST: Three second-line treatment options. IAS 2013.	PI/r + RAL vs PI/r + RAL induction for the first 12 weeks vs PI/r + 2 NRTIs	1277	96	The median VL was < 69,000	71	86 vs 61 vs 86[b]	No difference in adverse events between groups
Study 145 (ARV-experienced patients): 1) Elion, Molina. JAIDS 2013 2) Molina, Lamarca. Lancet ID 2012	EVG QD + OBT vs RAL BID + OBT	361 vs 363	48 96	26 vs 26	227 vs 215	59 vs 57.8 47.6 vs 45	23.7 vs 20.4 (the most commonly reported AE in both arms was diarrhoea)

OBT in BENCHMRK 1–2 was selected for each patient on the basis of previous ARV history and resistance testing (enfuvirtide, darunavir, and tipranavir could be included), and changes were permitted only for management of toxic effects or if patients switched to open label because of virological failure. OBT in SAILING varied in different patients. The most common background regimens were (DRV/r + TDF, LPV/r + TDF, DRV/r + ETR, LPV/r, ATV/r + TDF, DRV/r + MVC (ETR = etravirine and MVC = maraviroc). OBT in Study 145 was boosted PI + a third agent.

[a]In the SECOND-LINE study, viral load suppression was < 200 copies viral RNA/mL.

[b]In the EARNEST study, the outcome for viral load suppression was < 400 copies viral RNA/mL at week 96.

AE = adverse event; NRTI = nucleos(t)ide reverse-transcriptase inhibitor; PI = protease inhibitor; QD = once daily; VL = viral load. (See also Table I abbreviations.)

(32). After 96 weeks, the PI/RAL regimen was non-inferior to a PI plus 2–3 NRTIs, with 73% and 74%, respectively, of patients attaining plasma viral loads below 50 copies of viral RNA/mL (32). Another important conclusion of this study was that RAL was necessary in many cases to maintain virological control, as switching from PI/RAL to PI monotherapy after 12 weeks resulted in a decrease in virological success at week 96.

INSTIs were initially developed in response to the growing number of individuals living with multi-drug-resistant strains of HIV and who were no longer treatable with previous classes of inhibitors, including NRTIs, NNRTIs, and PIs (Table II). The BENCHMRK clinical trials showed that individuals infected with HIV resistant to NRTI, NNRTI, or PI and who failed previous treatments can be treated with RAL when given in combination with optimized background therapy (17,33–35). The long-term safety and efficacy of RAL in these patients was also demonstrated (10). At week 48 in the RAL arm, fewer than 50 copies of HIV RNA/mL were attained in 62.1% of patients versus 32.9% in the placebo arm. After prolonged treatment, the success rates were 57% versus 26% at week 96 and 51% versus 22% at week 156 in the RAL and placebo arm, respectively (17,33,35). In the BENCHMRK trial, subgroup analyses revealed a consistently favourable effect of RAL, regardless of virological load, CD4 + T-cell count, genotypic or phenotypic sensitivity score at baseline, or whether EFV, ritonavir-boosted darunavir (DRV/r) or both were included in the optimized background therapy (17,35). In contrast, another study performed in individuals who possessed characteristics similar to those of patients in the BENCHMRK trial showed an association between virological response to RAL and the number of active medications given with this drug (36). Different populations and statistical approaches may explain this discrepancy. In the Study 145, which is detailed below under 'Comparing integrase inhibitors', EVG and RAL were shown to have similar efficacy and safety in treatment-experienced patients who received these drugs in combination with one or two other active agents (37). DTG and RAL were also shown to be efficacious and safe for treatment-experienced patients with resistance to at least two classes of drugs (38). The results of this study are detailed below under 'Comparing integrase inhibitors'. Altogether, these studies and others have demonstrated the utility of INSTIs in the management of patients failing previous treatment.

Comparing integrase inhibitors

RAL is mostly cleared through glucuronidation by the UDP-glucuronosyltransferase UGT1A1 and can be administered in patients with severe renal and mild/moderate hepatic impairment (39). There are few drug–drug interactions between RAL and other anti-HIV agents, but rifampin co-administration requires a dose adjustment for RAL (40–42). In addition, RAL metabolism is not affected by race (43). Although several cases of severe skin reactions have been reported, there are no contraindications for the use of RAL.

It is also worth noting that RAL is given twice daily whereas both EVG/c and DTG can be taken once daily, the former because it is co-formulated with cobicistat as a booster and the latter because of a favourable pharmacokinetic profile. It has been argued that EVG co-formulation in a single pill with cobicistat, FTC, and TDF may make it advantageous for once-daily use compared to the twice-daily intake of RAL in regard to treatment adherence. In contrast, some patients may not be able to take a pharmacological booster for reasons of drug–drug interactions (30,44).

In addition, the co-formulation of EVG in a single tablet with cobicistat plus TDF/FTC explains the contraindication of this combination for patients with either renal impairment, co-infection with HBV, or who are being simultaneously treated with several other non-permissible, non-HIV-related drugs (30,44). DTG is contraindicated for use with the antiarrhythmic agent dofetilide and has been shown to cause a transient and moderate increase in serum creatinine, due to inhibition of tubular secretion without

Table III. Clinical trials comparing the use of different INSTIs.

Study	Regimen	Patients, *n*	Weeks of treatment	% With pretreatment viral load > 100,000 copies/mL	Median CD4 cell count at baseline (cells/mm^3)	HIV RNA < 50 copies/mL	% Adverse events related to drug
QDMRK: Eron J, Rockstroh J, Lancet 2011	RAL QD+ TDF/FTC vs RAL BID+ TDF/FTC	382 vs 388	48	39	24% (had < 200)	83.2 vs 88.9	7 vs 10
SPRING-2 (ARV-naïve patients):	DTG vs RAL	411 vs 411	48	27.7 vs 28.2	Data not available	88 vs 85	
1) Raffi, Jaeger. Lancet ID 2013	OBT: ABC/3TC or TDF/FTC		96			81 vs 76	No differences
2) Raffi, Rachlis. Lancet 2013							
Study 145:							
1) Elion, Molina. JAIDS 2013	EVG QD+ OBT vs RAL BID+ OBT	361 vs 363	48	26 vs 26	227 vs 215	59 vs 57.8	23.7 vs 20.4 (the most commonly reported AE in both arms was diarrhoea)
2) Molina, Lamarca. Lancet ID 2012			96			47.6 vs 45	
SAILING (ARV-experienced but INSTI-naïve patients): Cahn, Pozniak. Lancet 2013	DTG+ OBT vs RAL+ OBT	354 vs 361	48	Data not available	204 vs 193	71 vs 64	1 vs 1

OBT in Study 145 was PI/r + third agent. OBT in SAILING varied in different patients. The most common background regimens were DRV/r+ TDF, LPV/r+ TDF, DRV/r+ ETR, LPV/r, ATV/r+ TDF, DRV/r+ MVC.
OBT = optimized background therapy. (See also Table I abbreviations.)

affecting renal glomerular function (45,46). Importantly, a dose adjustment of DTG or the co-administration of ritonavir-boosted PIs might be required when DTG is prescribed in combination with etravirine, efavirenz, nevirapine, and two PIs (fosamprenavir and tipranavir). For several reasons, including treatment simplification and the drug–drug interactions that have been mentioned here, it is likely that DTG will be co-formulated with ABC and 3TC as a single tablet.

Another important drug that decreases levels of DTG and that is often used in HIV-infected patients is rifampin. No other relevant interactions with ARV drugs have been reported. In addition, RAL remains the only INSTI that caused fewer adverse events than EFV in two very-long-term clinical trials (15,16,18). Overall, RAL, EVG, and DTG are very well tolerated, with low toxicity and few adverse events.

INSTIs have also been compared for their antiretroviral activities. In the SAILING clinical trial, DTG was shown to be superior to RAL at week 48 in patients infected with viruses resistant to two or more antiretroviral drug classes, other than INSTIs, with 71% versus 64% success rates, respectively (Table III) (38). In the SPRING-2 clinical trials, however, DTG was 'only' non-inferior to RAL in treatment of drug-naïve individuals, with 88% versus 85% virological success, respectively, at week 48, and 81% versus 76% success after 96 weeks (28,29). No differences in numbers of adverse events were observed between the two arms. Additional studies have shown that ritonavir-boosted EVG given once daily with a PI and a third antiretroviral drug was non-inferior to twice-daily RAL in treatment-experienced individuals (37,47). At week 96, 47.6% and 45%, respectively, of treatment-experienced patients were successfully treated with QD EVG or BID RAL in combination with a boosted PI plus another antiretroviral agent (47). However, it should be noted that EVG is currently not co-formulated with a PI or ritonavir. No clinical trial has attempted to compare the safety and efficacy of the three INSTIs directly.

HIV resistance to INSTIs

Although RAL, EVG, and DTG appear largely equivalent in regard to their efficacy in therapy of treatment-experienced and -naïve individuals, there is an important difference between the two first-mentioned INSTIs and DTG in regard to HIV drug resistance. HIV can indeed develop resistance against both RAL and EVG in treatment-naïve and treatment-experienced patients who have failed therapy as a result of the emergence of discrete mutations in the integrase coding sequence (48,49). For RAL, major resistance mutations usually occur at positions Y143, N155, and Q148, whereas resistance to EVG is mostly associated with the emergence of mutations at positions T66, E92, N155, and Q148 (37,48–50). The broad cross-resistance profile between RAL and EVG precludes their sequential use in individuals failing either of them (Table IV).

Some of the mutations associated with HIV resistance to RAL and EVG, when combined with several other minor resistance mutations, can also decrease the ability of DTG to inhibit viral replication (51–53). In the VIKING clinical trial, 41% and 75% of patients who previously failed RAL-based regimens with the emergence of resistance mutations successfully responded to 50 mg DTG once and twice daily, respectively (52). Thus, DTG should be administered twice daily to patients who have previously failed treatment with RAL or EVG with emergent mutations. In addition, this study also revealed that patients with mutations at position Q148 plus additional mutations were more susceptible to fail treatment with DTG than patients with mutations at position N155 or Y143 (52). Similar results have been obtained after 24 weeks with patients who have failed RAL- or EVG-based regimens (54). Although 82% of all participants were successfully treated with DTG 50 mg administered BID after 8 days, success rates decreased to 69% and 48%, respectively, for patients with Q148 mutations plus one mutation and Q148 mutations plus at least two additional mutations. Although these results are very positive, considering that individuals enrolled in this study were infected with highly resistant HIV strains and had limited treatment options, they also demonstrated that patients are less likely to be successfully treated with DTG after they have failed therapy with RAL. Considering that the RAL and EVG resistance profiles overlap extensively, similar results can be expected for patients who have failed EVG.

More importantly, in treatment-naïve patients, DTG is the only antiretroviral drug for which no emergent resistance has been detected, even after protocol-defined virological failure. In the SAILING study, however, two study participants developed the R263K mutation after treatment failure with DTG (38). Another participant developed a mutation at position V151I/V that did not affect susceptibility to DTG, while another individual developed a T97A plus E138T/A combination of mutations subsequent to a Q148 mutation at baseline (38). Participants in this study were highly treatment-experienced, with resistance to two or more classes of antiretroviral drugs, and received one to two active drugs as part of their background therapy.

The extreme rarity of the emergence of HIV drug resistance mutation in patients failing DTG may be explained by laboratory studies that have shown that R263K is the most common emergent mutation in response to DTG drug pressure (55). Notably, in cell culture or in patients, DTG does not select for mutations commonly associated with resistance against RAL and EVG such as E92Q, Q148R/H/K, and N155H (51,55). In addition, there is no report of a secondary mutation that can adequately compensate for the diminished viral replication capacity and decreased enzyme activity associated with the R263K substitution (56,57). These results suggest that HIV may become resistant to DTG exclusively through the R263K substitution when the latter is used in first-line therapy, effectively leading the virus into an evolutionary dead-end. However, this hypothesis has not yet been proven, and further research will be required to evaluate this topic. Whether this hypothesis proves to be correct or not, it is indisputable that DTG possesses a barrier to resistance that is higher than that of either RAL or EVG, but primarily when it is used in first-line therapy.

The reason for this is probably that the generation of the R263K mutation is incompatible with the simultaneous presence of any of the primary mutations for RAL and EVG at any of positions 92, 143, 148, and 155. Indeed, work in our laboratory has shown that viruses that are engineered to contain R263K together with any of the latter RAL and EVG mutations are unable to grow.

It is also worth mentioning why the R263K substitution is preferentially selected by DTG, despite the fact that an accumulation of RAL and EVG mutations obviously confers much higher levels of drug resistance against DTG than does R263K. The reason is

Table IV. Major resistance mutations against RAL, EVG, and DTG.

T66I/A/K		EVG	
E92Q	RAL	EVG	
Y143R/C/H	RAL		
Q148H/R/K	RAL	EVG	DTG[a]
N155H	RAL	EVG	
R263K			?

[a]In combination with > 1 secondary mutations (commonly G140S/A/C and E138K/A/T).

probably that R263K alone results in a higher level of DTG resistance than do any of the mutations at positions 92, 143, 148, and 155. Although the level of resistance conferred by R263K is low, and probably not clinically significant, i.e. 2–5 fold, it is still higher than the levels of resistance that are conferred by the other four primary RAL and EVG mutations, which explains why it is selected in the place of the others. Then, the addition of a second mutation to R263K may lead to greatly diminished viral fitness, making it difficult for DTG-resistant viruses to replicate. As stated above, this hypothesis has not yet been proven, and further research on this topic will be required.

Conclusion

The development of INSTIs represents a compelling success in the history of biomedical research. These drugs are safe, efficacious, and well tolerated, and the field looks forward to the time that several members of this class will be available in the context of single tablet co-formulated regimen combinations that will be conveniently administered to patients on a once-daily basis. DTG is unique in its ability to avoid the emergence of drug resistance in treatment-naïve individuals, a characteristic that has no precedent in the history of ARV therapy. This unique property may also have relevance for public health strategies aimed at limiting or stopping the spread of HIV.

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