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Clinical effectiveness of dolutegravir in the treatment of HIV/AIDS

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Abstract: Dolutegravir (DTG) is a second-generation integrase strand transfer inhibitor (INSTI), which has now been licensed to be used in different countries including the UK. Earlier studies have demonstrated that DTG when used with nucleoside backbone in treatment-naïve and -experienced patients has been well tolerated and demonstrated virological suppression comparable to other INSTIs and superiority against other first-line agents, including efavirenz and boosted protease inhibitors. Like other INSTIs, DTG uses separate metabolic pathways compared to other antiretrovirals and is a minor substrate for CYP-450. It does not appear to have a significant interaction with drugs, which uses the CYP-450 system. Nonetheless, it uses renal solute transporters that may potentially inhibit the transport of other drugs and can have an effect on the elimination of other drugs. However, the impact of this mechanism appears to be very minimal and insignificant clinically. The side effect profiles of DTG are similar to raltegravir and have been found to be well tolerated. DTG has a long plasma half-life and is suitable for once daily use without the need for a boosting agent. DTG has all the potential to be used as a first-line drug in combination with other nucleoside backbones, especially in the form of a single tablet in combination with abacavir and lamivudine. The purpose of this review article is to present the summary of the available key information about the clinical usefulness of DTG in the treatment of HIV infection.

Keywords: dolutegravir, integrase inhibitors, HIV, antiretroviral, treatment

Introduction

The treatment of HIV infection is complex and changes rapidly as advances are made in basic science and clinical experience. Understanding of the different stages of viral replication and different enzymes used by the virus for their replication have helped to identify different agents that can block the function of the enzymes and thereby stop the viral replication inside host cells. Various events in the HIV life cycle plus host factors have been identified as potential targets for antiretroviral therapy.^{1,2} The complexity of treatment regimens against HIV infection increases further with the rising number of available compounds and the growth in new information about their use.

Drugs of five different classes are currently available in the developed world, with several others close to release. Inhibitors of HIV reverse transcriptase and of HIV protease are so far the most developed and most commonly used in clinical practice.³

Newer agents of these classes with better efficacy against the virus and sustained activity against viral resistance are in the pipeline of development. Drugs with longer half-life that penetrate in to different body compartments with less systemic side effects to the host are coming into production.⁴ Drugs with higher antiviral potency,

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less side effects, and simpler tablet regimens could improve the long-term treatment adherence and longer survival.⁵

Integrase (IN) has been a target for the drug development for sometime.⁶ Integrase strand transfer inhibitors (INSTIs) are one of the five classes of drugs and have demonstrated a potent antiviral activity⁷ and a noninferior efficacy versus regimens containing boosted protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) in treatment-naïve patients. INSTI-based regimens are among preferred options for first-line therapy for individuals with HIV-1 infection. Raltegravir (RAL), elvitegravir (EVG), and dolutegravir (DTG) all target the strand transfer step of viral DNA integration and are referred to as INSTI drugs. These are considered to be first line of treatment options in the Europe and the US.⁶

Dolutegravir – pharmacology, mode of action, and pharmacokinetics

DTG is a nitrogen-containing polycyclic compound possessing amide functionality and has two chiral centers, providing potential for stereoisomerism.⁸ It has been derived from the patent drug S/GSK1265744, which has one long-acting injecting formulation and an oral formulation developed as DTG.⁹

Mode of action

It is well known that integrase inhibitors (INTs, also known as integrase strand transfer inhibitors or INSTIs) represent a relatively new class of antiretroviral drugs to treat HIV-1 infection. It inhibits the incorporation of HIV-1 proviral DNA into the host cell genome, a step that is vital for viral replication. HIV IN is a 32 kDa protein that consists of three distinct structural and functional domains: the N-terminal domain, the catalytic core domain, and the C-terminal domain. It is the highly conserved catalytic triad, known as D64D116E152, which is believed to be responsible for the enzymatic activity.¹⁰

This enzyme catalyzes two vital chemical reactions known as 3' processing and strand transfer. During the first of the two steps, IN cleaves two terminal nucleotides from the 3' ends of both of the viral DNA strands to expose the invariant CA 3'-OH DNA ends. During the ensuing strand transfer step, IN is responsible for catalyzing the integration of viral DNA into the chromatin network of the host cell, using the freshly exposed 3'-OH ends to attack the phosphodiesterase backbone of the host cell DNA.^{9,10}

DTG inhibits the HIV IN by binding to the IN active site and blocking the strand transfer step of HIV DNA integration.

It fits loosely into the binding pocket of the intasome and undergoes conformational changes in the pocket structure while retaining its binding ability. The ability to make adjustment in the binding capacity is potentially favorable compared to other INSTIs.^{11,12}

Pharmacokinetics

DTG has favorable pharmacokinetic properties and retains plasma concentrations well above the protein-adjusted 90% inhibitory concentration (IC₉₀) for HIV-1.^{11,13}

Absorption

DTG is rapidly absorbed following oral administration. The median maximum plasma concentration (C_{max}) is achieved 1.5–2.5 hours after oral intake with a mean half-life of 12–15 hours, rendering feasible for once-daily dosing without the need for pharmacological boosting. Bioavailability varies with fat content. Song et al¹⁴ demonstrated that food intake increased DTG exposure and reduced the rate of absorption. Healthy subjects received DTG (50 mg) in a single-dose crossover study while they were in the fasted state or with low-, moderate-, or high-fat meals. The area under the plasma concentration–time curve (AUC) from 0 hour to infinity hours increased by 33%, 41%, and 66% when administered with low-, moderate-, or high-fat meals, respectively, compared with the fasting state. However, the increase in DTG exposure is not expected to impact clinical safety and, thus, can be taken with or without food and without considering the fat content of the food.^{11,14}

Distribution

DTG has got high affinity for plasma proteins, and >99% of DTG is bound to plasma proteins, and it is independent of the plasma concentration. DTG has good penetration to other body compartments and appears to cross the blood–brain barrier; however, clinical outcomes have not been determined. The apparent volume distribution of DTG following oral absorption appears to be around over 12.5 L, which is comparable to the level seen after intravenous administration. This in turn suggests that the drug has a very low first-pass metabolism.¹³ DTG is present in other body compartments, including cerebrospinal fluid and cervicovaginal fluid. After oral dosing, DTG exposure in cervicovaginal fluid was found to be 5%–7% of blood plasma exposure compared to around 200% for RAL. In semen, the DTG concentration is 6%–7% of blood plasma concentration compared to over 400% of ritonavir (RTV). The exposure in colorectal tissue is 18%–20% of the blood

plasma concentration. It could be due to the fact that DTG is highly protein bound, and the amount of free drug present may be adequate and comparable to in vitro IC₉₀. DTG exposure in cerebrospinal fluid was similar to unbound plasma concentrations in blood plasma.^{11,13}

Metabolism

DTG is extensively metabolized in the liver using the Phase II metabolism primarily through glucuronidation via UGT1A1, while a minor pathway (in Phase I) involves CYP450 3A4 (CYP3A4) with other minor pathways (Phase II) involving UGT1A3 and GT1A9.¹⁵

Elimination

The terminal half-life is about 14 hours. The apparent oral clearance is about 1 L/h. Fifty-three percent of the total oral dose of DTG is excreted unchanged in the feces, 32% through urine as glucuronide (18%) or alkylated product (3.5%), and other organic conjugated products resulting from Phase II liver metabolisms. About 1% of unchanged DTG is excreted through urine, rendering it relatively safer to use in mild or moderate renal impairment.¹⁵

Dolutegravir – clinically significant drug interactions

DTG has the potential to interact with other medicinal products, including antiretrovirals, but they appear to be clinically insignificant in most of the cases.^{15,16} DTG is metabolized by the uridine diphosphate glucuronosyltransferase (UGT) enzyme system (Phase II liver metabolism).¹⁷ Coadministration of drugs or medicinal agents that use UGT1A1, UGT1A3, and UGT1A9 may alter the blood level of DTG, and some of the interactions may have clinical implications (Table 1).^{11,17}

DTG is a minor substrate for the CYP-P450 system (Phase I metabolism); however, this could potentially be altered when used along with drugs that has major effect on CYP-450 system, especially CYP-45 3A4.

Coadministration with drugs using *p*-glycoprotein and breast cancer resistance protein may alter the blood level of DTG as well but no clinically significant interaction has been reported. DTG uses the organic cation transporter (OCT) system in renal tubules and can increase the blood level of OCT2-dependent drugs.¹⁸ DTG and the pharmacological booster cobicistat are the two examples of well-characterized

Table 1 Key drug interactions of dolutegravir

Interacting drug class	Interacting drug	Effect on dolutegravir or interacting drug concentration	Dose recommendation	
Antiretrovirals	NRTIs	TDF	No significant effect was observed	No change in dose
	NNRTIs	EFV	Significant reduction in DTG plasma concentration	Increase dose of DTG to 50 mg twice daily
		ETR	Significant reduction in DTG plasma concentration	Do not administer DTG with ETR alone
		ETR/DRV/RTV	No significant effect was observed	DTG and ETR can be used only if DRV/r is also included in the regimen
PIs	ATV/r	Increase in DTG plasma concentration	No change in dose	
Acid-reducing agents				
	Bivalent cations including calcium, iron, or zinc supplements, or with vitamin-D supplements	Significant reduction in DTG plasma concentration, but no interaction with PPI	Administer antacids or bivalent containing supplements 2 h after or 6 h before DTG dosing	
Antituberculous agents				
	RIF	Significant reduction in DTG plasma concentration	Increase the DTG dosing frequency to 50 mg twice daily	
	RBT	No significant effect was observed	No change in dose	
Oral contraceptives				
	Ortho-cyclen	No significant effect was observed	No change in dose	
Antihepatitis C virus agents				
	PIs	BCV	No significant effect was observed	No change in dose
		TRV	No significant effect was observed	No change in dose
Opioid agonist				
	Methadone	No significant effect was observed	No change in dose	

Note: Data from the following studies.^{11,16,18,21,22,25,39,40}

Abbreviations: ATV/r, atazanvir/ritonavir; BCV, boceprevir; DTG, dolutegravir; DRV/RTV, darunavir/ritonavir; EFV, efavirenz; ETR, etravirine; h, hour; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; RBT, rifabutin; RIF, rifampin; TDF, tenofovir disoproxil fumarate; TRV, telaprevir.

mechanisms of creatinine transporter inhibition in the proximal tubule. While DTG inhibits mainly the renal transporter OCT2 in the basolateral membrane of the proximal tubular cell, cobicistat predominantly inhibits the renal transporter MATE1 in the luminal membrane,^{18–20} thereby increasing the blood level of creatinine without impairing the true glomerular filtration rate. DTG can interact with oral medicinal agents, such as antacids containing bivalent cations, and the interaction of DTG with bivalent cations²¹ appears to be physical in the form of chelation and, hence, can reduce the blood level of DTG (Table 1).

Interaction with specific groups

Antiretrovirals

Similar to RAL, DTG is metabolized primarily by UGT1A1, so the number and type of drug–drug interactions (DDIs) are expected to be comparable to those seen with RAL.¹¹

Drug interaction between nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and DTG is very minimum and clinically insignificant.¹¹ Tenofovir disoproxil fumarate (TDF), a NRTI that is primarily eliminated by renal mechanisms, does not have any significant interactions with DTG, and these two drugs can be taken together without dose adjustment (Table 1).

Because NNRTIs display a complicated interaction outline and have the potential to induce both the major and minor metabolic pathways of DTG, one would expect a reduced DTG plasma concentration if these drugs were coadministered.^{22,23} When DTG is combined with efavirenz (EFV), there is a decrease in AUC, C_{max} , trough plasma concentration (C_{trough}) by 57%, 39%, 75%, respectively, hence, the recommended dose of DTG is 50 mg twice daily when coadministered with EFV.²³

When DTG was combined with etravirine (ETR) in healthy volunteers, ETR significantly decreased exposures of DTG (AUC and C_{trough} was decreased by 70% and 88%, respectively).²⁴ When ETR was combined with a RTV-boosted PI, the interaction was reversed. But ETR/lopinavir (LPV)/RTV treatment had no effect on the DTG plasma AUC_{0–} and C_{max} , whereas the plasma concentration increased by 28%. Combination of ETR/darunavir (DRV)/RTV modestly decreased the plasma DTG AUC_{0–}, C_{max} , and plasma concentration by 25%, 12%, and 37%, respectively.^{25,26} Such effects of ETR/LPV/RTV and ETR/DRV/RTV do not appear to have any clinical relevance.²⁴ The combination of DTG and ETR alone should be avoided, but it may be coadministered with ETR without a dose adjustment if DTG and boosted PIs is concurrently administered.²⁴

Coadministration of DTG with boosted PIs has been studied in randomized trials, and data demonstrate that DTG can be coadministered with PIs without dose adjustment. DTG was combined with atazanavir (ATV)/RTV and ATV in a randomized, open-label, two period's crossover study in healthy adults. The results showed modest, nonclinically significant increase in DTG exposure (Table 1). But no dose adjustment for DTG was required when coadministered with ATV and ATV/RTV, and it was well tolerated.²⁷

Similarly, when DTG was coadministered with LPV/RTV there was no clinically significant effect on the steady-state plasma concentration of DTG and again it showed good tolerability (Table 1). Although coadministration of DRV/RTV resulted in decreased steady-state plasma DTG exposures, the effect is not anticipated to be of clinical significance.²⁶

Antacids, calcium, and iron supplements

Polyvalent cations, particularly bivalent cations, including calcium, iron, or zinc supplements as well as other cations present in antacids, it may chelate DTG and reduce its efficacy.^{21,28} Administering antacids at the same time with DTG lowers DTG AUC and minimum plasma concentration (C_{min}) by 74%. To evade this interaction, DTG should be given at least 2 hours before or 6 hours after administering polyvalent cations (Table 1). Gastric pH does not seem to have any effect on DTG absorption and is not known to have any interaction between DTG and proton pump inhibitors.^{21,22}

Rifamycin compounds

Rifampin (RIF) is a potent inducer of CYP450 (3A4) and UGT1A1. RIF (600 mg) lowers DTG AUC and C_{min} by 54% and 72%, respectively; administering RIF with 50 mg of DTG twice daily results in DTG levels that are comparable to those seen when DTG is dosed at 50 mg once daily without concomitant RIF (Table 1). Therefore, the DTG dosage should be increased to 50 mg twice daily for IN-naïve patients receiving concomitant RIF.²⁹

Rifabutin (RBT) lowers DTG C_{min} by 30% but does not significantly change the AUC or C_{max} . Based on these data, RBT (300 mg once daily) may be coadministered with 50 mg of DTG once daily.²⁹

Direct-acting hepatitis C virus antivirals

Use of boceprevir (BCV) and telaprevir (TRV) with DTG has been investigated in healthy volunteers in an open-label study. Coadministration of BCV (800 mg every 8 hours) and DTG

(50 mg once daily) increased DTG C_{max} , AUC, and C_{trough} by 5%, 7%, and 8%, respectively. This interaction is of no clinical significance (Table 1). Similarly, TRV increased DTG AUC, C_{max} , and C_{trough} by 25%, 19%, and 37%, respectively, by the inhibition of CYP3A. When compared to historical controls, there was no effect on TRV exposure. Hence, no dose adjustment is necessary when DTG is combined with direct-acting antivirals.³⁰ DTG has not been found to have any significant interaction with grazoprevir and elbasvir, newer antivirals for treating hepatitis C virus.³¹

Other agents

DTG may be given with estrogen/progestin oral contraceptives without dose adjustment and was well tolerated when combined with these compounds (Table 1).³²

Available data^{8,11} does not support any possibility for DTG to cause clinically significant DDIs with 3-hydroxy-3-methyl-glutaryl-co-enzyme A reductase inhibitors such as simvastatin, rosuvastatin, and atorvastatin.

Dofetilide is a class III antiarrhythmic agent (available in the US in capsules containing 125 µg, 250 µg, and 500 µg of dofetilide and not available in Europe and Australia) has the potential to interact with DTG.^{33–35} The use of DTG can increase dofetilide level or affect by inhibiting the renal OCT2, and thereby increasing the blood level of dofetilide. There is a risk of life-threatening arrhythmias when DTG is used with dofetilide, and hence, coadministration of these two drugs is contraindicated.^{33,36} Coadministration of DTG and metformin was well tolerated. In a study using healthy volunteers, coadministration of DTG and metformin was well tolerated, but significantly increased metformin plasma exposure, and the effects were DTG dose dependent. Although metformin has a wide therapeutic index and alone is not associated with hypoglycemia, close monitoring is recommended when coadministering metformin and DTG.³⁷

DTG and prednisone coadministration was well tolerated. No dose adjustment is essential for DTG when coadministered with prednisone.^{8,38,39} DTG can be taken with or without food in treatment-naïve and INSTI-naïve patients. However, in treatment-experienced patients in the presence of INSTI class resistance, DTG should preferably be taken with food to enhance the exposure.¹⁴ Methadone use has not been found to have any interaction with DTG and dose adjustment for methadone or DTG is not recommended.⁴⁰

Efficacy studies of dolutegravir

DTG use has been studied in HIV treatment-naïve and experienced patients and the results are mostly very much

favorable, standing it relatively ahead of other antiretrovirals (Table 2). In SPRING-1,⁴¹ a treatment-naïve, Phase IIb randomized dose-ranging multicenter, partially blinded study, DTG demonstrated sustained efficacy and a favorable safety and tolerability profile. In this study, adults with HIV-1 infection who were treatment-naïve were randomized to DTG 10 mg, 25 mg, or 50 mg once daily or 600 mg of EFV once daily (control arm) combined with investigator-selected dual nucleos(t)ide reverse transcriptase inhibitor (NRTI), backbone regimen TDF/emtricitabine (TDF/FTC), or ABC/3TC. The primary goal of SPRING-1 was to select a DTG dose for Phase III development. A rapid and sustained antiviral response was detected across all DTG doses, with 82% of all participants who received DTG attaining plasma HIV-1 RNA <50 copies/mL through week 96. The safety profile of DTG at 96 weeks was favorable, with no dose-response relationship with adverse events (AEs). Tolerability, in general, was also better with DTG in comparison with EFV. There was no protocol-defined virological failure in participants receiving 50 mg of DTG or resistance mutations to INSTIs or NRTIs, and the 50 mg dose was selected for Phase III evaluation. DTG demonstrated a sustained efficacy and a favorable safety and tolerability profile in a treatment-naïve Phase IIb randomized dose-ranging multicenter, partially blinded study.

The SINGLE study,⁴² a head-to-head randomized, double-blind, Phase III study comprised treatment-naïve adults with HIV-1 infection, and the participants were allocated to DTG 50 mg combined with ABC/3TC once daily or in combination therapy with single pill Atripla containing TDF, FTC, EFV once daily. At 48 weeks, 88% of the DTG group achieved viral load suppression <50 copies/mL, in comparison to 81% suppression in the Atripla group. Statistical analysis demonstrated that the DTG regimen performed significantly better than Atripla ($P=0.003$) and met the criterion for statistical superiority. Virological failure was 4% in both arms. Results were similar for participants with different baseline viral load levels (above or below 100,000 copies/mL). The DTG regimen was associated with a significantly higher rise in CD4 cells compared to the Atripla group (267 cells/mm³ vs 208 cells/mm³, respectively, $P<0.001$). Differences in efficacy were primarily driven by a lower rate of discontinuation due to AEs for the DTG plus ABC/3TC arm and were independent of baseline viral load. Treatment-related discontinuation was 2% in the DTG arm compared to 10% in the EFV arm. The safety profile of the DTG arm in general was more favorable when compared to the Atripla arm. No patients in the DTG arm developed INSTI or NRTI resistance, whereas

Table 2 Key efficacy studies of dolutegravir

Naïve studies	Participants (N)	Design	Duration	Comparing arm	VL <50 (%)	Conclusion
SINGLE ⁴²	844	Randomized 1:1	144 wk	DTG 50 mg + ABC/3TC EFV/FTC/TDF	80% 72%	DTG superior to EFV No treatment-emergent resistance in DTG arm
SPRING-2 ⁴³	822	Randomized 1:1	96 wk	DTG 50 mg + two NRTIs RAL 400 mg BD + two NRTIs	81% 76%	DTG was noninferior to RAL No additional resistance to INSTIs or NRTIs since week 48 in DTG arm
FLAMINGO ⁴⁵	484	Randomized 1:1	96 wk	DTG 50 mg + two NRTIs DRV/RTV + two NRTIs	82% 52%	DTG superior to DRV/RTV at 96 wk. Difference most pronounced at baseline VL >100,000 copies/mL
Experienced studies						
SAILING ⁴⁶	715	Randomized 1:1	48 wk	DTG 50 mg + two NRTIs RAL 400 mg BD + NRTIs	71% 64%	Treatment-emergent INSTIs resistance (four in DTG arm) vs (17 in RAL arm). DTG superior to RAL (P=0.03).
VIKING-3 ⁴⁸	183	Single-arm study	24 wk	DTG 50 mg BD + (continuing a failing regimen [without RAL or EVG] 7 days) optimized ≥ 1 fully active drug and DTG continued	69%	Reduced response with Q148 + ≥ 2 resistance mutations DTG 50 mg BD-based therapy was effective in highly treatment experience with INSTI-resistance
VIKING-4 ⁴⁹	30	Randomized 1:1	24 wk	DTG 50 mg BD, 7 days on failing regimen without RAL or EVG vs placebo DTG	40% no drop	DTG 50 mg BD-based therapy was effective in INSTI failing regimen

Abbreviations: ABC/3TC, abacavir/lamivudine; DRV/RTV, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; INSTIs, integrase strand transfer inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; RAL, raltegravir; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; wk, weeks; VL, viral load; BD, twice a day.

one patient on Atripla developed NRTI resistance and four patients developed NNRTI resistance.⁴²

At 96 weeks of follow-up, DTG plus ABC/3TC remained superior to EFV/TDF/FTC. No major treatment-emergent INSTI or NRTI resistance mutations were detected through 96 weeks with DTG plus ABC/3TC. In this study, 50 mg of DTG combined with ABC and 3TC once daily as a single pill was superior to single pill Atripla in treatment-naïve HIV-1 patients.⁴²

In SPRING-2,⁴³ a 96-week, Phase III, randomized, double-blind, active-controlled, noninferiority study, treatment-naïve adults with HIV-1 infection were randomly assigned (1:1) to receive either DTG (50 mg) once daily or RAL (400 mg) twice daily. Study drugs were given with coformulated TDF/FTC or ABC/3TC. The primary endpoint was the proportion of participants with HIV-1 RNA <50 copies/mL at 48 weeks, with a 10% noninferiority margin.⁴³

The primary analysis of the SPRING-2 study⁴³ at week 48 demonstrated that 88% of patients in the DTG arm achieved an HIV-1 RNA of <50 copies/mL compared to 85% in the RAL arm (adjusted difference 2.5%; 95% CI: -2.2 to 7.1). AEs were similar between the two treatment groups. There was no evidence of treatment-emergent

resistance in patients with virological failure on DTG, whereas for the patients with virological failure who received RAL, one had INSTI treatment-emergent resistance and four had NRTI treatment-emergent resistance. DTG has a noninferior efficacy and similar safety profile compared to RAL.⁴³ At week 96 analysis in SPRING-2 study, once-daily DTG was noninferior to the twice-daily RAL arm with 81% of patients in the DTG arm and 76% of patients in the RAL arm having HIV-1 RNA <50 copies/mL (adjusted difference 4.5%, 95% CI: -1.1% to 10.0%) and confirmed noninferiority. Median increases in CD4 cell count from baseline were similar between the groups (276 cells/ μ L for DTG and 264 cells/ μ L for RAL). No study-related serious AEs occurred between week 48 and week 96. Ten patients in each group discontinued because of AEs. In those who had virological failure, no additional resistance to INSTIs or NRTIs was detected since week 48.⁴⁴ In this randomized double-blind study, DTG has shown a similar efficacy, tolerability, and safety profile to another first-line INSTI.⁴⁴

The FLAMINGO study⁴⁵ is a multicenter, open-label, Phase IIIb, noninferiority study. Treatment-naïve adults with HIV-1 infection were randomly assigned (1:1) to receive

50 mg of DTG once daily or 800 mg of DRV plus 100 mg of RTV100 once daily, with investigator-selected TDF/FTC or ABC/3TC. No study participants had primary reverse transcriptase or protease mutations upon enrolment, and all had a viral load above 1,000 copies. The primary endpoint was the proportion of patients with HIV-1 RNA concentration <50 copies/mL at week 48 with a 12% noninferiority margin.

Analysis at week 48 showed 90% of patients in the DTG arm and 83% of patients on the DRV plus RTV arm had HIV-1 RNA of <50 copies/mL. The adjusted difference of 7.1% (95% CI: 0.9%–13.2%) confirmed the superiority of DTG to DRV/RTV in antiretroviral-naïve adults ($P=0.025$). Virological failure was similar in both arms, with no treatment-emergent resistance recorded in either group. Median CD4 gain was similar in both treatment arms. Results, however, among those with baseline viral loads >100,000 copies/mL favored DTG. There was less discontinuation due to AEs in the DTG arm (2%) than for DRV plus RTV (4%) and that may have contributed to the difference in response rates. Once-daily DTG was numerically and statistically superior to once-daily DRV plus RTV in patients with baseline viral load >100,000 copies/mL; however, those in the stratum below 100,000 copies results were quite comparable. In the FLAMINGO study, DTG demonstrated for the second time that it is superior to another recommended first-line antiretroviral agent.⁴⁵

SAILING is a 48-week, Phase III, randomized, double-blind, active-controlled, noninferiority study involving adults who are on failing antiretroviral therapy with ongoing viral replication, resistance to two or more classes of antiretroviral drugs, and had one to two fully active drugs for background therapy.⁴⁶ They had not been previously exposed to INSTIs. Participants received 50 mg of DTG once daily or 400 mg of RAL twice daily, with investigator-selected background therapy. The primary endpoint was the proportion of patients with plasma HIV-1 RNA <50 copies/mL at week 48, while secondary endpoint was the proportion of patients with treatment-emergent INSTIs resistance. At week 48 of follow-up, 71% of patients on DTG had HIV-1 RNA <50 copies/mL versus 64% of patients on RAL (adjusted difference 7.4%, 95% CI: 0.7–14.2); confirming superiority of DTG against RAL ($P=0.03$). Significantly fewer patients had virological failure with treatment-emergent INSTIs resistance on DTG (four vs 17 patients; adjusted difference –3.7%, 95% CI: –6.1 to –1.2; $P=0.003$). AE frequencies were similar across both groups. Once-daily DTG had greater virological efficacy compared to twice-daily RAL in this treatment-experienced patient group and was well tolerated. The statistical

superiority demonstrated in the DTG arm was driven by fewer withdrawals due to lack of efficacy, lower number of protocol-defined virological failures, and lower treatment-emergent resistance.

The safety and efficacy of DTG in treatment-experienced subjects with RAL-resistant HIV-1 infection have been assessed in the VIKING study.⁴⁷ In this study, individuals received 50 mg of DTG once daily (Cohort I) or 50 mg twice daily (Cohort II) while continuing the failing regimen (without RAL). After day 10, the background regimen was optimized where feasible for Cohort I and at least one fully active drug was mandated for Cohort II. The primary endpoint was the proportion of subjects on day 11 with ≥ 0.7 log₁₀ copies/mL plasma HIV-1 RNA reduction below baseline or <400 copies/mL. Ninety-six percent of subjects in Cohort II and 78% of subjects in Cohort I achieved the primary end point (ie, a reduction in plasma HIV-1 RNA level of ≥ 0.7 log₁₀ copies/mL below the baseline value or a level of <400 copies/mL on day 11. Fifty-four percent in Cohort II and 41% in Cohort I achieved an HIV-1 RNA level of <400 copies/mL on day 11.⁴⁷ At week 24, the response rate was greater in Cohort II, 75% had a plasma HIV-1 RNA level of <50 copies/mL, in contrast to 41% in Cohort I.⁴⁷ The response rates increased in both cohorts as the number of fully active agents in the optimized background regimen was added.

DTG has also been assessed in antiretroviral-experienced patients with RAL- and/or EVG-resistant HIV-1: VIKING-3⁴⁸ and VIKING-4⁴⁹ study (Table 2). VIKING-3 is a single-arm, open-label Phase III study in which INSTIs-experienced adults with INSTI-resistant virus received DTG 50 mg twice daily while continuing their failing regimen (without RAL or EVG and resistance to ≥ 2 ART classes other than INSTIs). Through day 7, the regimen was optimized with one or more fully active drug and DTG continued. Over the 8-day monotherapy period, it was obvious that DTG demonstrated activity against viruses that have INSTI resistance.⁴⁴ The greatest result was seen in those with a history of INSTI resistance but no INSTI resistance mutations at baseline. These patients had a drop in HIV-1 RNA of 1.5 log₁₀ copies/mL ($P<0.001$). At week 24, 74% of patients had viral loads below 400 copies/mL and response maintained at week 48. Those who had one INSTI mutation with Q148 still had a good response, but slightly less than those with no mutations. However, the effect was reduced when Q148 was paired with ≥ 2 INSTI mutations. Safety profile on DTG 50 mg twice daily was similar to that with DTG 50 mg once daily.^{45,46} Another study⁵⁰ has investigated

whether DTG-resistant viruses are impaired in their ability to acquire further resistance to other agents such as NRTIs and NNRTIs as a consequence of their relative inability to develop resistance mutations associated with these two compounds. In this study,⁵⁰ the investigators examined the ability of DTG-resistant viruses containing either the R263K or G118R and/or H51Y mutations to develop further resistance against several reverse transcriptase inhibitors during *in vitro* selection experiments. The investigators were able to show that mutations in the R263K and G118R resistance pathways delay the emergence of resistance mutations against reverse transcriptase inhibitor and suggest that the presence of mutations associated with resistance to DTG can impair the ability of HIV to acquire further resistance against nevirapine and 3TC, a NNRTI, and NRTI, respectively.⁵⁰ These findings may be in line with the conception that R263K may not be a deleterious mutation for DTG in contrast to the mutations in the RAL/EVG pathways that have the ability to severely compromise DTG activity.⁵⁰

The recently presented data by Granier et al⁵¹ from pooled analysis of three different naïve studies (SINGLE, SPRING-2, and FLAMINGO) have demonstrated the superiority of virological efficacy over comparator in two of the three-naïve studies. These pooled analyses suggested no evidence of a difference in long-term virological efficacy between DTG and third agents or between ABC/3TC and TDF/FTC at low or high viral load.

Resistance

DTG has been considered to have a higher genetic barrier and minimal cross-resistance compared to other INSTIs.⁵² The major mutations that reduced DTG antiviral efficacy *in vitro* were I151L, T66K/L74M, G140/Q148R, G140/G148R, and E138K/Q148R. There was an increase in susceptibility from 3.5- to 8.4-fold change in susceptibility, but the isolates still retain the susceptibility to DTG. The combination of mutations at E138K and Q148R results in a tenfold decrease in DTG susceptibility compared to a 140–330-fold susceptibility to RAL and 370–390-fold susceptibility to EVG.⁵¹ These data suggest that DTG may still retain antiviral activity against virus resistant to other two INSTIs. Underwood et al has shown that patients failing with RAL with mutations at Y143 or N155 can retain activity with DTG.⁵³ But those with Q148 and additional INSTI mutations should decrease susceptibility to DTG. There are few other mutations like H51Y, which potentially may reduce DTG activity but they are very rare and unlikely to appear and further studies may delineate more information. The resistance data from the

available clinical studies have so far shown that multiple IN mutations plus a mutation at Q148 are necessary to reduce DTG activity.^{54–56} In the presence of INSTI resistance, the dose of DTG should be increased to 50 mg twice daily as has been used in VIKING-3⁴⁸ and VIKING-4⁴⁹ studies.

Dolutegravir: adverse effects, safety, and tolerability

DTG has revealed a favorable safety profile in Phases II and III trials (Table 3). In the SPRING-1 study, there were no dose-related patterns in type, frequency, or severity of AEs across DTG doses, and most events reported in the DTG groups were of mild (48%) or moderate (34%) intensity. Only 2% of individuals in the SINGLE trial withdrew from the DTG arm due to AEs, compared to 10% from the EFV arm.^{41,42} In SPRING-2, DTG and RAL were equally tolerated with only ten patients (2%) in each group discontinuing because of AEs. No study-related serious AEs occurred between week 48 and week 96. Nausea, headache, diarrhea, and sleep disturbances were the most common AEs being reported by individuals taking DTG (Table 3). Blood levels of DTG in the randomized clinical trials⁵⁶ were not correlated with the presence of the most frequent AEs, including diarrhea, nausea, and headache or with most clinical laboratory tests of interest.^{43,57,58} The most common laboratory abnormalities reported in the clinical trials were increased cholesterol (Figure 1), lipase, bilirubin, aspartate transaminase/alanine transaminase, creatine phosphokinase, and prothrombin time, as well as decreased phosphate and neutrophil count.^{41,42,56} Patients with underlying hepatitis B or C may be at increased risk of worsening or development of transaminase elevations with the use of

Table 3 Dolutegravir adverse effects grades 2–4 in treatment-naïve trials

Side effects	Range (%)	Comments
Gastrointestinal	2–17	Diarrhea and nausea were the most common GI side effects, mainly mild-to-moderate in severity
Headache	1–15	Mainly mild in nature
Insomnia	1–4	Were typically mild in intensity
Rash	1	Were significantly low in most of the studies (generalized macular rash, maculopapular rash, pruritic rash)
Liver abnormality	2–3	Alternative causes for raised ALT identified in few patients. Very few patients had DTG-associated DILI with hypersensitivity reaction
Nasopharyngitis	<1	Mild in nature

Note: Data from the following studies.^{41–45}

Abbreviations: DTG, dolutegravir; DILI, drug-induced liver injury; GI, gastrointestinal; ALT, alanine transaminase.

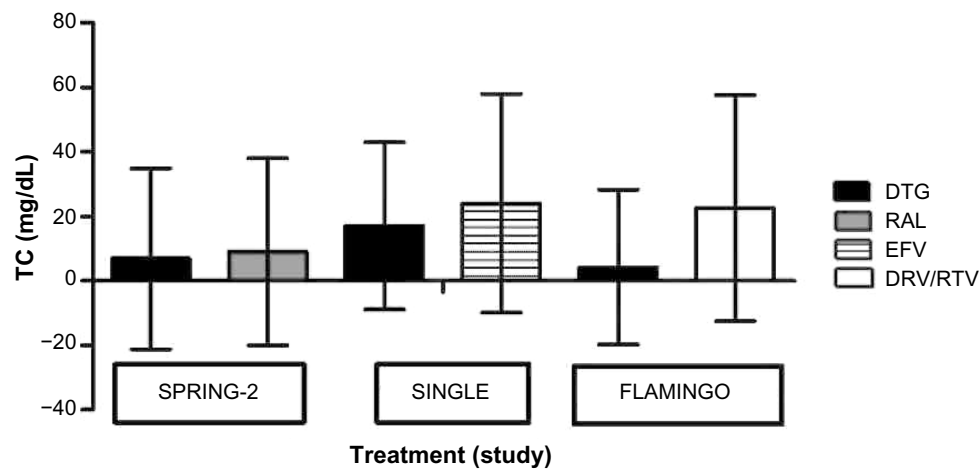


Figure 1 Mean TC changes from baseline at 48 weeks.

Abbreviations: DRV/RTV, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; RAL, raltegravir; TC, total cholesterol.

DTG. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation, particularly in the setting where antihepatitis therapy was withdrawn. The AEs did not appear to be related to plasma DTG exposure.

Overall, DTG is well tolerated, with headache and insomnia being the most frequently reported AEs. A systematic review by Patel et al⁵⁹ has demonstrated that DTG use was associated with a relatively lower risk of AEs and less risk of withdrawal from studies due to AEs compared to other antiretrovirals including EFV, boosted PIs, but no difference compared to RAL and rilpivirine use (Table 3).

Hypersensitivity reactions have been reported in <1% of subjects receiving DTG in Phase III randomized controlled clinical trials.^{41,42} More over DTG when used in a combination product with ABC and 3TC marketed as triumeq has the

potential to have hypersensitivity reactions as seen in ABC use alone. Clinically, it is unlikely to be differentiated whether the reaction is due to ABC or DTG.

Effect of dolutegravir on lipids

DTG appears to be lipid neutral. In comparative analysis from the SINGLE, SPRING-2, and FLAMINGO studies, DTG demonstrated a generally neutral effect on serum lipid changes irrespective of nucleoside backbone (Figures 1–4).^{59,60} The total cholesterol/high-density lipoprotein ratio remained similar in all the groups (Figure 5). This is comparable to the similar effect seen with other INSTIs, namely, RAL. In a systematic review, Patel et al⁵⁹ showed that DTG use was associated with lower rise of total cholesterol, low-density lipoprotein cholesterol, and triglyceride compared to EFV and boosted PIs, including ATV, DRV, and LPV.⁶⁰

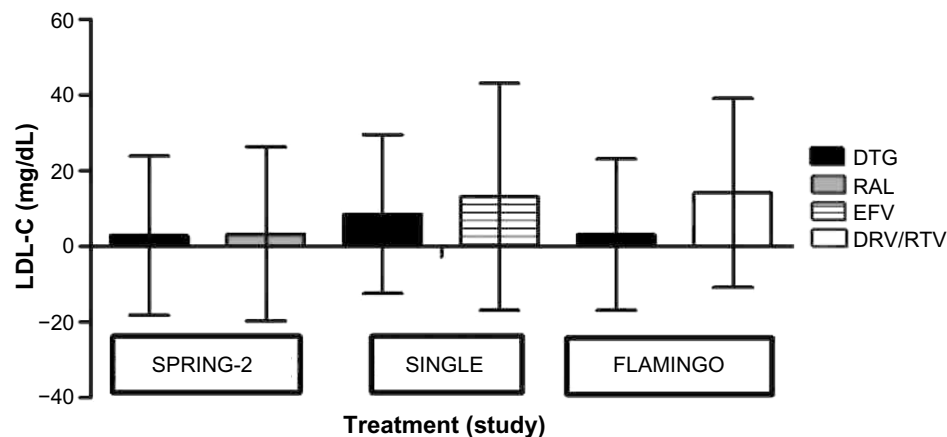


Figure 2 Mean LDL-C changes from baseline at 48 weeks.

Abbreviations: DRV/RTV, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; LDL-C, low-density lipoprotein cholesterol; RAL, raltegravir.

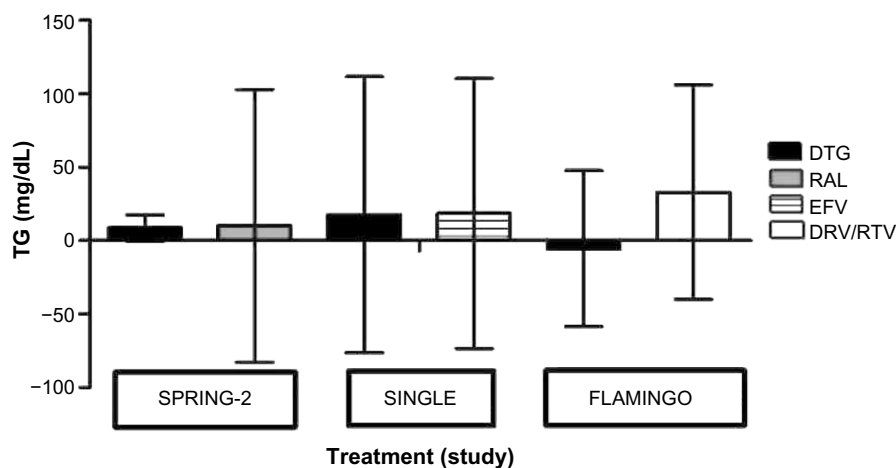


Figure 3 Mean TG changes from baseline at 48 weeks.

Abbreviations: DRV/RTV, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; RAL, raltegravir; TG, triglyceride.

Effect on bone health

DTG like other INSTIs appears to have less effect on bone health. In SINGLE study after 48 weeks of follow-up, bone markers were increased in both groups, but the increases were significantly higher in the Atripla group. Vitamin-D levels are decreased in both the arms, but the differences were not different.⁶¹ The BMD changes as demonstrated by DEXA scan did not reveal any difference in DTG use.⁶¹ Recently presented data from the study after 144 weeks of follow-up have shown an increased turnover of bone markers in the Atripla arm compared to the DTG arm. Vitamin-D levels were similar in both groups.⁶²

Use in special population

DTG so far appeared to be safe and well tolerated in both treatment-naïve and treatment-experienced patients. In the

absence of more robust information, caution should be taken in specific populations (Table 4).

Dolutegravir – patient perspectives quality of life, patient satisfaction and acceptability, adherence

There are important factors to think of when deciding whether a given regimen should be considered a “recommended” option for a first-line therapy such as efficacy, tolerability, and convenience of taking the drug, which all play important roles.³ This also includes, drug–drug and drug–food interactions, as well as baseline patient-specific factors such as CD4+ cell count,³ plasma HIV-1 RNA level, child-bearing potential (in women), and a range of comorbidities, including viral hepatitis coinfection.⁶³ All three INSTIs are now included within the treatment guidelines for

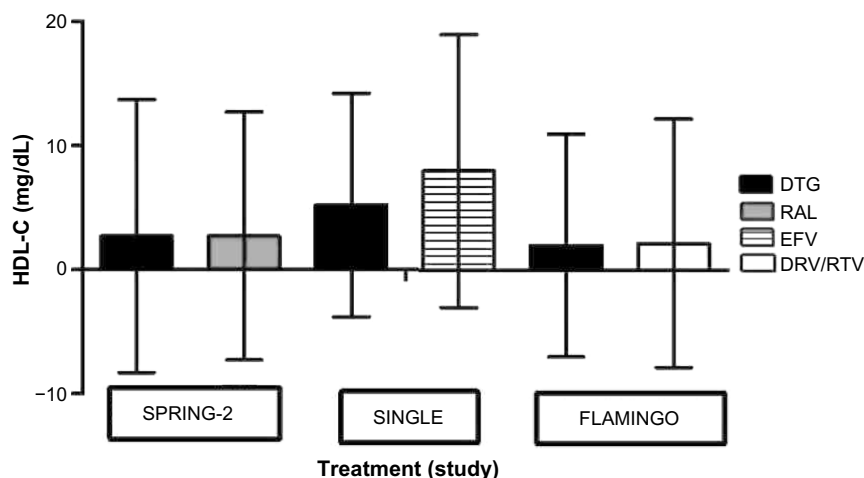


Figure 4 Mean HDL-C changes from baseline at 48 weeks.

Abbreviations: DRV/RTV, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; HDL-C, high-density lipoprotein cholesterol; RAL, raltegravir.

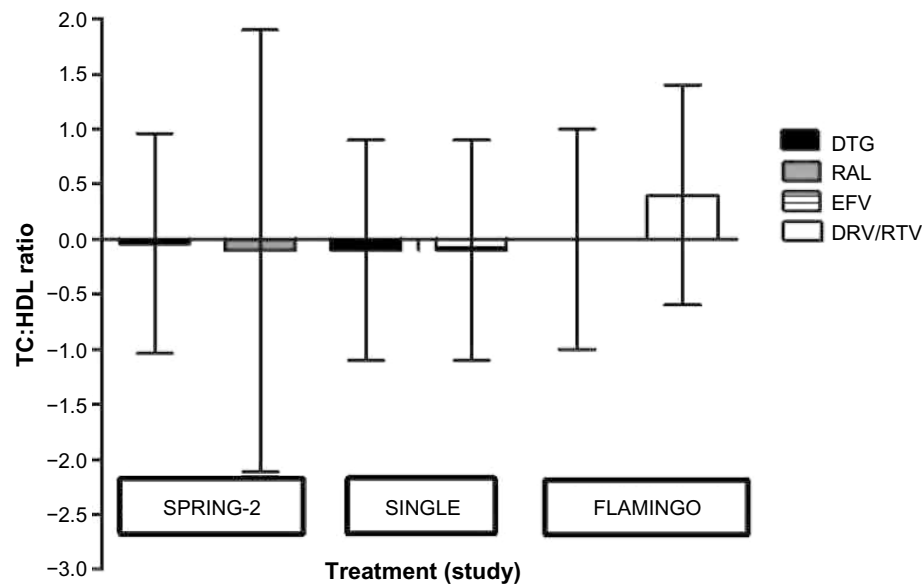


Figure 5 TC:HDL ratio changes from baseline at 48 weeks.

Abbreviations: DRV/RTV, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; RAL, raltegravir; TC:HDL, total cholesterol:high-density lipoprotein.

the adult HIV patients.³ In randomized controlled studies, DTG has shown superiority over two other commonly used third agents, EFV and boosted DRV. DTG has a novel resistance profile, it has shown activity against HIV-1 isolates with INSTI-resistant strains with no emergent resistance to date with first-line DTG failure. DTG is metabolized by UGT1A, with minimal contribution from cytochrome P450 (3A4 isoform) and limiting DDI.¹¹ DTG has a prolonged intracellular half-life; thus, once-daily dosing without the need for pharmacological booster is acceptable if taken with or without food.^{8,11} INSTIs are potent agents, well tolerated with favorable metabolic profiles and few DDIs (RAL, DTG). Despite the rates of transmitted (baseline) drug resistance to INSTIs alleged to be low, resistant phenotypes

have been reported for both RAL and EVG.⁶⁴ Certain mutations confer cross-resistance between both agents (RAL and EVG), but DTG has a better resistance profile and so far appears to have relatively higher genetic barriers.^{46,65}

Pill burden, twice daily regimen, relation of food and content of food, taking pills at particular time of the day had all been factors with antiretrovirals.^{66,67} DTG has the potential to overcome all these barriers and can be taken once daily as a single pill at any time of the day without the need for food. This has the potential advantage of giving patients the liberty to take medications at their choice, not compromising with their daily life promising a better quality of life. Moreover, HIV patients are living longer and when polypharmacy is common in patients in aged

Table 4 Use of dolutegravir in special population

Conditions	Findings	Comment
Pregnancy	Categorized as pregnancy category B. No adequate and well-controlled studies in pregnant women because animal reproduction studies are not always predictive of human response. ^{8,72}	To be used with caution.
Nursing mother	In animal studies DTG was present in rat milk, human data are not available. ⁷²	No clear evidence.
Pediatric	Safety and efficacy of use of DTG has not been established in pediatric patients younger than 12 years and weighing <40 kg.	No clear evidence.
Elderly	The data of safety in patients aged over 65 years is very limited.	To be used with caution.
Renal	The plasma concentration of DTG was found to be decreased in subjects with severe renal impairment compared to those in the healthy controls; however, no dose adjustment was necessary where renal impairment was mild-to-moderate. ^{73,74} No data on renal dialysis patients.	Caution in severe renal impairment.
Hepatic	There have not been any differences between subjects with moderate hepatic impairment and hepatic subjects. ^{63,75,76}	No dose adjustment in mild or moderate hepatic impairment.
Hepatitis B and C coinfection	DTG can be safely used with boceprevir and telaprevir. ^{30,63}	No dose adjustment.

Abbreviation: DTG, dolutegravir.

population,⁶⁸ less pill burden and minimal drug interaction appears to be a distinct advantage of DTG compared to others.⁶⁹ The debate of using DTG with ABC in patients with high-risk cardiovascular disease remains and that has to be dealt with on an individual patient level.^{70,71} INSTI-based regimens may be appropriate for many (if not most) treatment-naïve patients and DTG represents a new option for INSTIs-experienced patients.

Conclusion

DTG is an INSTI that maintains a high plasma level and supports a once-daily dosing regimen without the need for a pharmacokinetic boosting agent. DTG in combination with ABC and 3TC has developed a single-tablet regimen for the treatment of HIV infection. Such treatment could have the potential to be advantageous over the other combination antiretroviral agents available as a single tablet. As there is very minimal effect on Phase I liver metabolism involving CYP-pathway, it is unlikely to interact with other antiretroviral agents and a very minimum interaction with other commonly used medicinal agents.

Although there is potential for the interaction at renal tubular level involving OCTP, the clinical significance so far appeared to be very minimum. DTG, the third INSTI, appears comparable to or better than guideline-approved first-line antiretroviral agents with potent antiviral activity. DTG remains the agent with good tolerability and better patient safety. It has multiple clearance pathways and little clinically significant pharmacokinetic variability, and it has also a predictable exposure–response relationship. DTG has the advantage of being a once-daily tablet, with a small milligram dose and tablet size. Although the size of the combination tablet containing DTG, ABC, and 3TC named as trumeq is not smaller than the available single-pill regimen, it has been well tolerated in all the randomized control trials and appeared to be safe and effective. DTG has the potential to become the first-line antiretroviral agent, with a strong prospect of offering a good quality of life for the patients.

Author contributions

HT and SD jointly did the literature search and appraised the papers. HT prepared the first draft. AD did further literature search, revised the paper, and helped in citations and preparing the tables and figures. SD conceived the idea and supervised the whole paper. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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