Dolutegravir: clinical efficacy and role in HIV therapy

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***Abstract*:** The human immunodeficiency virus type-1 (HIV-1) integrase enzyme has recently emerged as a primary alternative target to block viral replication, and integrase strand transfer inhibitors (INSTIs) are now considered an alternative 'third agent' class of antiretroviral (ARV) drugs. Dolutegravir is the first next-generation INSTI showing some novel and intriguing characteristics: it has a favorable pharmacokinetic profile with a prolonged intracellular halflife, rendering feasible a once daily dosing without the need for pharmacokinetic boosting. Secondly, it is largely metabolized *via* uridine diphosphate glucuronosyltransferase-1A1 with a minor component of cytochrome P450 isoforms, thus allowing a low grade of drug–drug interactions, so that its metabolic profile consents co-administration with the majority of the other ARV drugs without dose adjustments. Lastly, but no less important, virological studies have clearly demonstrated that dolutegravir has a significant activity against HIV-1 isolates showing raltegravir and/or elvitegravir associated resistance mutations. The attributes of once daily administration and the potential to treat INSTI-resistant viruses make dolutegravir an interesting and promising new agent in the treatment of both naïve and experienced HIV-1 subjects. In this review, the main concerns on dolutegravir efficacy are focused through the analysis of the currently available data from clinical studies in naïve and experienced patients, evaluating its possible place within the anti-HIV-1 drug armamentarium. The development of newer once daily, single tablet coformulations improved drug adherence and maximized the success of ARV therapy. Pharmacokinetic studies and dose-ranging trials suggested that dolutegravir is a good candidate for a single tablet regimen in one or more new coformulated pills that will be available in the near future.

Keywords: antiretroviral drugs, dolutegravir, HIV-1, integrase inhibitors, once-daily dosing

Introduction

The significant advances in the treatment of human immunodeficiency virus type-1 (HIV-1) infection during the past 15 years have led to a dramatic reduction in HIV-1 related morbidity and mortality. The potency, tolerability and convenience of the latest antiretroviral (ARV) agents have considerably improved and made easier the lifelong treatment of HIV-1. Despite the success of existing therapies in controlling viral replication and preventing disease progression, ARV therapies are not curative, thus remaining a permanent commitment for HIV-1 infected patients [Palella *et al.* 1998; Antiretroviral Therapy Cohort Collaboration 2008; van Sighem *et al.* 2010]. Moreover, long-term positive effects of combined ARV treatments (cART) are often complicated by the occurrence of drug resistance (mainly in non-adherent subjects) and/or drug-related side effects and metabolic toxicities. There is a need for simplified regimens that provide a lower pill burden, a reduced dose frequency and a more favorable safety profile [Juday *et al.* 2011].

There are five classes of drugs that fight against HIV-1 infection (Table 1). Each class has a name that comes from the mechanism of action against the virus: nucleos(t)ide reverse transcriptase inhibitors [N(t)RTIs]; non-nucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PIs); entry inhibitors and antagonists of the CCR5 chemokine receptor; and integrase strand transfer inhibitors (INSTIs). The standard of care for treatment of HIV-1 infection involves

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Table 1. List of the currently used antiretroviral drugs and marketed coformulations.

NRTIs	NNRTIs	PIs	INSTIs	Entry inhibitors	Coformulated options
Zidovudine, ZDV Lamivudine, 3TC Abacavir, ABC Tenofovir, TDF Emtricitabine, FTC Didanosine, ddI Stavudine, d4T Zalcitabine, ddC (no longer used)	Efavirenz, EFV Nevirapine, NVP Etravirine etR Rilpivirine, RPV Delavirdine, DLV (no longer used)	Indinavir, IDV Saquinavir, SQV Nelfinavir, NFV Fosamprenavir, FPV Lopinavir, LPV Atazanavir, ATV Darunavir, DRV Ritonavir, RTV (as booster only)	Raltegravir, RAL Elvitegravir, EVG (as coformulation only) Dolutegravir, DTG	Enfuvirtide (T-20) Maraviroc, MVC	ZDV/3TC ZDV/3TC/ABC LPV/r ABC/3TC TDF/FTC TDF/FTC/EFV TDF/FTC/RPV TDF/FTC/EVG/COBI

COBI, cobicistat; INSTIs, integrase strand transfer inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleos(t)ide reverse transcriptase inhibitors; PIs, protease inhibitors.

Table 2. Recommended first-line regimens: DHHS and EACS guidelines update, October 2013.

	DHHS		EACS
	Preferred regimens	Alternative regimens	Recommended regimens
NNRTI	EFV/TDF/FTC	EFV + ABC/3TC RPV/TDF/FTC or RPV + ABC/3TC	EFV or RPV + ABC/3TC or TDF/FTC
Boosted PI	ATV/r + TDF/FTC DRV/r + TDF/FTC	ATV/r + ABC/3TC DRV/r + ABC/3TC FPV/r + (TDF/FTC or ABC/3TC) LPV/r + (TDF/FTC or ABC/3TC)	ATV/r or DRV/r + ABC/3TC or TDF/FTC
INSTI	RAL + TDF/FTC EVG/COBI/TDF/FTC DTG + ABC/3TC DTG + TDF/FTC	RAL + ABC/3TC	RAL + TDF/FTC or ABC/3TC

3TC, lamivudine; ABC, abacavir; ATV, Atazanavir; COBI, cobicistat; DHHS, Department of Health and Human Services; DTG, dolutegravir; DRV, darunavir; EACS, European AIDS Conference Society; EFV, efavirenz; EVG, elvitegravir; FPV, fosamprenavir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; r, ritonavir; RPV, rilpivirine; LPV, lopinavir; RAL, raltegravir; TDF, tenofovir di-fumarate.

the use of a combination of at least three ART drugs belonging to different classes [Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013; EACS, 2013]. Coformulated options, and even more, once-daily single tablet regimens represent the best cART simplification achieved so far (Table 2). They include drugs with favorable pharmacokinetics that allow once-daily administration, that do not need dose adjustments, have no additional toxicities, and do not require dissimilar intake conditions [Llibre and Clotet, 2012].

N(t)RTIs have traditionally been an important 'backbone' of almost all ART regimens. However, concerns about long-term toxicities and a cross-resistance pattern within the N(t)RTI class combined with the continuing development of newer, apparently safer agents of different classes has led to an increasing interest in the potential use of feasible, innovative and more appealing N(t)RTI-sparing options [Achhra and Boyd, 2013]. PIs constitute an important component of cART in the light of their potency and higher genetic barrier that they impose against the selection of drug resistance variants [Kempf *et al.* 1997; De Meyer *et al.* 2005]. PIs are the only class of ARV drugs that have been used as monotherapy and shown to be not inferior to cART regimens in maintaining suppression of viral replication [Bierman *et al.* 2009; Perez-Valero and Arribas, 2011].

INSTIs are a new class of ARV drugs designed to block the action of the integrase viral enzyme, which catalyzes several key steps in the HIV-1 lifecycle and is responsible for insertion of the viral genome into the DNA of the host. Because integration is a crucial step in retrovirus

replication machinery, the viral enzyme has become an attractive molecule for the treatment of HIV-1 infected patents [Reinke *et al.* 2002; Pommier *et al.* 2005]. Inhibitors of this enzyme represent the new class of ARV agents available in our armamentarium to treat HIV-1 infection [Hazuda *et al.* 2000].

Raltegravir (RAL) was the first drug of the INSTI class approved by the US Food and Drug Administration (FDA) in 2007; it is a potent and well-tolerated antiviral agent. When combined with other active agents, it has demonstrated similar virological efficacy up to 240 weeks to the combination of efavirenz (EFV), tenofovir (TDF) and emtricitabine (FTC) in treatment-naïve patients [Markowitz *et al.* 2011; Rockstroh *et al.* 2013]. However, RAL has the limitations of twice-daily dosing and a relatively modest genetic barrier to the development of resistance. Another first-generation INSTI is elvitegravir (EVG), available in a single tablet regimen and dosed once daily when administered with ritonavir (RTV) or the pharmacokinetic booster cobicistat (COBI), a potent CYP3A4 inhibitor that can lead to clinically significant drug–drug interactions. Also this drug shows a low genetic barrier as RAL, with an overlapping resistance profile. Following the results of larger studies comparing a fixed-dose formulation consisting of EVG/COBI/FTC/TDF *versus* a EFV/TDF/FTC single tablet regimen or a once-daily RTV-boosted atazanavir (ATZ) plus FTC/TDF, the new single tablet EVG/COBI/FTC/TDF (Stribild®) is available in several countries for the once-daily treatment of HIV-1 infection in ARV therapy-naïve adults [Perry, 2014].

Both RAL and EVG are now guideline-preferred agents as part of an ARV regimen for treatment-naïve patients. However, the above-mentioned proprieties of RAL and EVG have prompted the search for new agents with once-daily dosing, a high genetic barrier and a resistance profile of limited overlap with the respect of the first-generation INSTIs [Karmon and Markowitz, 2013].

Dolutegravir (DTG, S/GSK1349572) is a new (next-generation) drug in this class that offers some novel and intriguing characteristics: it has a favorable pharmacokinetic profile with a prolonged intracellular halflife, rendering feasible a once-daily dosing without needs of pharmacokinetic boosting and without regard to meal. It also offers a favorable resistance profile showing a higher genetic barrier to resistance compared to the other INSTIs. Table 3 summarizes the main characteristics of the currently available INSTIs.

The primary route of DTG metabolism is its glucuronidation *via* uridine diphosphate (UDP) glucuronosyl-transferase (UGT) 1A1, without a significant induction or inhibition of cytochrome P450 (CYP) isoenzymes [Min *et al.* 2010]. DTG has a terminal elimination halflife of 13–14 h and maintains concentrations over the *in vitro*, protein-adjusted IC90 for more than 30 h following a single dose. DTG exhibits rapid absorption, with a median time to the maximum plasma concentration (t_{max}) ranging from 0.5 to 2 h. DTG also displays extensive protein binding, with 99% of the DTG blood plasma concentrations being bound to albumin and α1-acid glycoprotein (AAG) [Cottrell *et al.* 2013; Underwood *et al.* 2012; Canducci *et al.* 2011]. DTG exhibits lower intersubject pharmacokinetic variability than other integrase inhibitors. DTG is a substrate for the transporters P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP), but does not demonstrate inhibition or induction of the transporters Pgp, BCRP, organic anion transporter (OAT)-P1B1, OATP1B3, multidrug resistance protein (MRP)-2 or cation transporter transporter (OCT)-1 at clinically relevant concentrations. DTG potently inhibits the renal organic OCT2 at concentrations below the peak concentrations demonstrated in clinical trials. DTG use over 48 weeks of therapy does not appear to impact renal function, although the long-term effects of DTG on renal function are still unknown [Reese *et al.* 2013]. DTG absorption is modestly affected by the fat content of a meal. Phase II and III investigations to date have not employed food restrictions for DTG dosing. Only a small proportion of the drug dose (<1%) is excreted unchanged in the urine and, therefore, DTG is not expected to require dose adjustments in subjects with renal impairment [Min *et al.* 2011].

INSTI resistance pattern

Drug resistance mutations have been reported for all currently approved anti-HIV drugs, including the latest INSTIs. Resistance to INSTIs occurs with a single point mutation within the integrase gene. The three most common RAL mutations (N155H, Q148H/K/R and Y143C/H/R) are associated with virological failure and reduced susceptibility to RAL [Cooper *et al.* 2008]. If the virus harbors one or more of these mutations, crossresistance between RAL and EVG can occur.

Table 3. Main characteristics of INSTIs currently used in clinical practice.

	Recommended dose	Metabolism	Advantages	Disadvantages
RAL	400 mg BID	UGT1A1-mediated glucuronidation	- Fewer CNS adverse effects - Few drug–drug interactions - No food restrictions	- No FDC available - Inferior to DTG in treatment-experienced patients - Low genetic barrier
EVG	150 mg QD + booster (100 mg ritonavir or cobicistat) to be taken with meals	Predominantly cytochrome P450 (CYP3A4) metabolized, minor pathways *via* UGT1A1/3 glucuronidation and oxidative metabolism	- Fewer CNS adverse effects, less rash, and better lipids than EFV - Non inferior to RAL in treatment-experienced patients - Once-daily administration with COBI	- Not recommended for patients with eGFR <70 ml/min - Must be taken with food - Low genetic barrier - Many COBI-related drug–drug interactions
DTG	50 mg QD in INSTI-naïve patients, 50 mg BD in INSTI-experienced patients	Predominantly UGT1A1-mediated glucuronidation, cytochrome P450 (CYP3A4) metabolisation as minor pathway	- Fewer CNS and rash events - Few drug–drug interactions - Small mg dose and tablet size - No food restrictions - Once-daily administration	- Not yet available as part of FDC - Inhibits tubular secretion of creatinine

BID, twice daily; CNS, central nervous system; COBI, cobicistat; DTG, dolutegravir; eGFR, estimated glomerular filtration rate; EVG, elvitegravir; FDC, fixed dose combination; INSTI, integrase strand transfer inhibitor; QD, once daily; RAL, raltegravir; UGT, uridine diphosphate glucuronosyltransferase.

The next-generation INSTI DTG shows a more robust resistance profile than RAL and EVG. An *in vitro* study demonstrated that the highest genetic barrier of DTG may be attributed to its significantly slower rate of dissociation from the integrase enzyme in viruses that are either wildtype or contain the N155, Q148 or Y143 mutations [Hightower *et al.* 2011]. Furthermore, DTG may undergo slight conformational change at the active site to overcome the physical barrier created by these single point mutations [Hare *et al.* 2011]. These properties are probably responsible for the effectiveness of DTG against most RAL/EVG resistant strains, although viruses containing E138K, G140S or Q148H mutations had lower susceptibility [Quashie *et al.* 2012b]. Exposure to DTG in selection studies can cause changes in the viral genome at positions E92, L101, T124, S153 and G193 [Kobayashi *et al.* 2011]. However, susceptibility fold changes are moderate (<2.5) for all these substitutions. Although no major resistance mutations against DTG have been identified thus far, the accumulation of multiple mutations is required to result in a fold change >10. *In vitro* selection studies revealed R263K, followed by H51Y, as the most common mutation to emerge. Further analyses showed that R263K did confer low-level resistance to DTG in culture, with an approximate 20–30% loss in viral replication fitness. H51Y alone did not significantly affect either strand transfer activity or resistance. The presence of both mutations increased levels of resistance to DTG, but this combination rarely emerged due to severe attenuation of both viral replicative capacity and integrase strand transfer activity compared with the presence of R263K alone [Quashie *et al.* 2012a; Mesplede *et al.* 2012]. Recently, biochemical and structural data reported that the G118R substitution caused low-level resistance to DTG (3.1-fold), and the addition of H51Y to G118R did not significantly increase the level of resistance (3.4-fold). The combinations of G118R together with multiple other substitutions might result in an enzyme that most likely would be catalytically defective [Quashie *et al.* 2013]. Furthermore, DTG-resistant viruses containing either the R263K or G118R and/or H51Y mutations were unable to develop further resistance mutations against several reverse transcriptase inhibitors during *in vitro* selection (i.e. nevirapine and lamivudine). These findings may explain the fact that no individual has yet progressed to virological failure with DTG resistance mutations in clinical trials in which patients received the drug together with an optimized background regimen [Oliveira *et al.* 2014]. In cell cultures, the emergence of the resistance mutation R263K followed by the polymorphic substitution M50I has been observed.

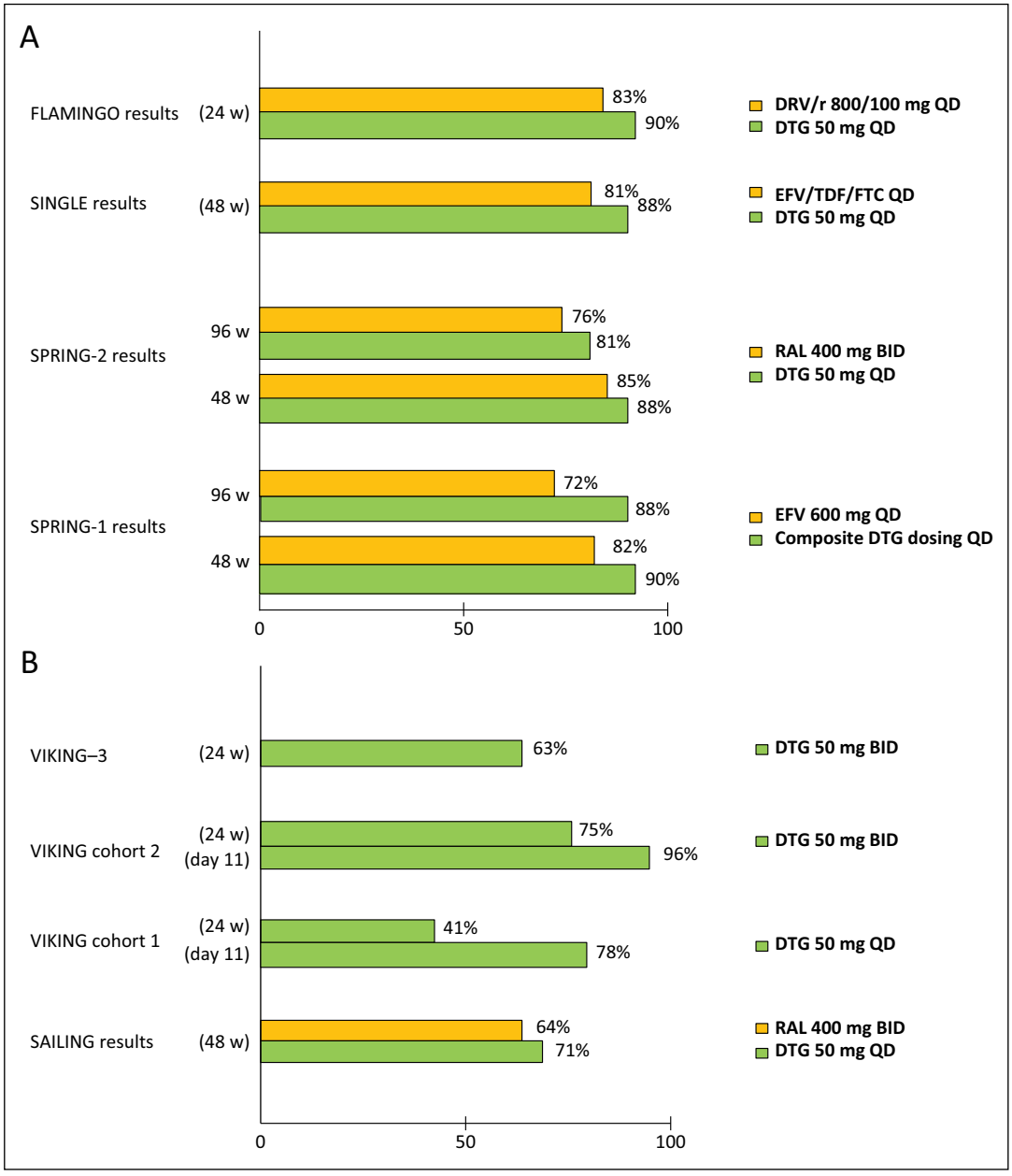

Figure 1. Virological response rates from DTG studies in naïve (A) and experienced (B) HIV-1 patients.
BID, twice daily; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; HIV, human immunodeficiency virus; QD, once daily; RAL, raltegravir; TDF, tenofovir.

This polymorphism has also been described in 10–25% of patients naïve to INSTIs and in one subject (in combination with the R263K mutation) failing a RAL-based regimen. The M50I polymorphism in combination with R263K increases resistance to DTG in tissue culture and in biochemical assays, but does not restore the diminished viral fitness associated with the R263K mutation. This combination results in a virus with limited crossresistance, so the R263K resistance pathway may represent an evolutionary dead end. According to these *in vitro* findings, it may be more advantageous to use DTG in a first-line strategy rather than in a more advanced setting [Wares *et al*. 2014].

Clinical efficacy of DTG

The virological outcomes of the main DTG studies reported are detailed in Figure 1.

Results from studies in naïve subjects

SPRING-1 was a 96-week, randomized, partially blinded, phase IIb dose-ranging study to evaluate the efficacy and safety/tolerability of DTG. Treatment-naïve HIV-1 infected patients were randomly assigned to receive DTG 10, 25, or 50 mg once daily or EFV 600 mg once daily (control arm) combined with investigator-selected dual NRTI backbone regimen (TDF/FTC or ABC/3TC). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA <50 copies/ml, based on time to loss of virological response at 16 weeks (conducted for the purpose of phase III dosing selection), with a planned analysis at 96 weeks. Briefly, 205 patients received study drug and the rate of plasma HIV-1 RNA <50 copies/ml at week 96 was 79%, 78%, and 88% for subjects on DTG (10, 25, and 50 mg, respectively), compared with 72% of those on EFV. The median increase from baseline in CD4+ T cells was 338 cells/µl with DTG (all treatment groups combined) compared with 301 cells/µl in EFV group. No clinically significant dose-related trends in adverse events were observed and fewer participants who received DTG withdrew because of adverse events (3%) compared with EFV group (10%). Nausea and headache occurred more frequently with DTG, whereas dizziness, rash, insomnia and fatigue were more common in EFV arm. Consistent with the findings observed, DTG demonstrated slightly more rapid and sustained virological suppression when compared with EFV [van Lunzen *et al*. 2012; Stellbrink *et al.* 2013].

In another study (SPRING-2) DTG was compared to RAL in a 96 week, phase III, randomized, double-blind, active-controlled, noninferiority study in treatment-naïve adults with HIV-1 RNA levels ≥1000 copies/ml; enrolled subjects were randomly assigned (1:1) to receive either DTG (50 mg once daily) or RAL (400 mg twice daily). Randomization was stratified by screening HIV-1 RNA plasma levels (> or ≤100,000 copies/ml) and NRTI backbone [TDF/FTC or abacavir (ABC)/lamivudine (3TC)]. A total of 822 subjects received at least one dose of the study drug (411 patients in each group). At week 96, 332 (81%) patients in the DTG group and 314 (76%) patients in the RAL group had HIV-1 RNA <50 copies/ml, thus confirming the DTG noninferiority *versus* RAL. Virological nonresponse occurred less frequently in the DTG group [22 (5%) patients for DTG *versus* 43 ([10%)] patients for RAL]. Within treatment groups, virological nonresponse was similar for ABC/3TC and TDF/FTC. Median increases in CD4+ T cell count from baseline were similar between groups (276 cells/µl for DTG and 264 cells/µl for RAL). At virological failure, no additional resistance to INIs or NRTIs was detected since week 48 or in any patient receiving DTG [Raffi *et al.* 2013b]. The tolerability and safety of DTG and RAL were similar in terms of frequency and nature of adverse events through 96 weeks. Patients receiving DTG had small mean increases in serum creatinine (grade 1–2) that were evident by week 2 and remained stable through week 96 [Raffi *et al.* 2013a]. Results from the SPRING-1 and 2 studies clearly show that once-daily DTG-based therapy is an attractive treatment option for HIV-1-infected treatment-naïve patients.

SINGLE was a 48-week, randomized, double-blind, phase III study on HIV-1 infected ART-naïve adults who had an HIV-1 RNA level ≥1000 copies/ml. Participants were randomly assigned to DTG 50 mg plus ABC/3TC once daily or fixed-dose combination therapy with EFV/TDF/FTC (Atripla®). The primary endpoint was the proportion of participants achieving HIV-1 RNA levels <50 copies/ml at week 48 [intention-to-treat analysis (ITT)]. Secondary endpoints included the time to viral suppression, the change from baseline in CD4+ T cell count, safety profile and viral resistance pattern. A total of 833 subjects received at least one dose of study drug. At week 48, the proportion of participants with an HIV-1 RNA level <50 copies/ml was significantly higher in the DTG plus ABC/3TC group than in the EFV/TDF/FTC group (88% *versus* 81%, $p = 0.003$), thus meeting the criterion for superiority. Overall differences in response were due primarily to discontinuations because of adverse events (2% in the DTG plus ABC/3TC group *versus* 10% in the EFV/TDF/FTC group). The difference in the treatment response in favor of DTG plus ABC/3TC was observed among participants indifferently from the baseline HIV-1 RNA levels (> or ≤100,000 copies/ml); treatment differences were also maintained across key demographic characteristic subgroups. Moreover, the DTG plus ABC/3TC arm presented a shorter median time to viral suppression than did the EFV/TDF/FTC group (28 *versus* 84 days, $p < 0.001$), as well as a greater increase in CD4+ T cell count (267 *versus* 208 cells/µl, $p < 0.001$). No subject in the DTG arm had detectable resistance mutations; one TDF-associated mutation and four EFV-associated mutations were detected in patients with virological failure in the EFV group [Walmsley *et al.* 2013].

Recently the FLAMINGO study results were reported. This is a randomized, multicenter, open-label, noninferiority study on HIV-1 infected ART-naïve adults with HIV-1 RNA ≥1000 copies/ml and no N(t)RTIs or PIs resistance mutations. Patients were randomized 1:1 to receive DTG 50 mg once daily or darunavir/ritonavir (DRV/r) (800/100 mg once daily with an investigator-selected fixed dose combination backbone (TDF/FTC or ABC/3TC). Randomization was stratified by HIV-1 RNA plasma levels (≤ or >100.000 copies/ml) and NRTI backbone. The primary endpoint was the proportion of patients reaching HIV-1 RNA <50 copies/ml through week 48 by FDA snapshot analysis. A total of 484 patients (242 in each arm) were treated. At week 48, 90% of DTG and 83% of DRV/r patients had HIV-1 RNA <50 copies/ml, thus demonstrating the superiority (p = 0.025) of once daily DTG according to a prespecified testing procedure. A more pronounced treatment difference occurred in individuals with higher baseline viral loads. In the DTG arm, no statistically significant differences were observed in terms of virological response according to the background dual NRTI strata. No treatment emergent genotypic resistance occurred in either arm at the time of virological failure. In terms of laboratory abnormalities, the serum creatinine in DTG recipients increased 0.1–0.2 mg/dl, attributable to DTG's inhibition of renal tubular secretion of creatinine *via* OCT2. No other laboratory abnormalities of clinical significance were reported. Increases in fasting LDL were somewhat higher in the DRV/r group [Feinberg *et al.* 2013; Clotet *et al.* 2013].

These preliminary results reinforce the role of DTG as a new first-line option in the treatment of HIV-1 infected subjects. In all studies in which DTG has been compared with the currently approved standards of care (EFV, DRV/r and RAL), results have demonstrated virological efficacy rates comparable with each of these gold standard agents, with comparably low rates of adverse effects and (remarkably) no emergence of integrase resistance at failure reported.

Results from studies in experienced subjects

To assess whether DTG retained activity in the face of ARV resistance, different studies have been conducted: the SAILING study in ARV-experienced, INSTI-naïve subjects (*versus* RAL); and the VIKING studies in ARV-experienced subjects harboring a virus with RAL/EVG resistance patterns.

The SAILING study was a 48-week, phase III, randomized, double-blind, active-controlled, noninferiority study. Eligible patients were ARV-experienced and INI-naïve, had two consecutive plasma HIV-1 RNA assessments ≥400 copies/ml (unless those with ≥1000 copies/ml at screening), resistance to two or more classes of ARV drugs, but at least one to two fully active drugs for background therapy. Patients were randomly assigned (1:1) to once-daily DTG 50 mg or twice-daily RAL 400 mg, with investigator-selected background therapy. Analysis included 715 patients (354 in the DTG group and 361 in the RAL group). At week 48, 71% of patients on DTG arm had HIV-1 RNA <50 copies/ml *versus* 64% of those on RAL arm, with a significant virological superiority of DTG *versus* RAL (p = 0.03). Fewer patients had virological failure with treatment-emergent INSTI resistance on DTG (four *versus* 17 patients; p = 0.003). Once-daily DTG, in combination with up to two other ARV drugs, was well tolerated with a greater virological effect compared with twice-daily RAL in this selected treatment-experienced, INSTI-naïve patient group [Cahn *et al.* 2013].

The VIKING study (including cohorts 1 and 2) was a single-arm phase II trial that analyzed the feasibility of an INSTI salvage therapy by replacing RAL 400 mg twice daily with DTG 50 mg once or twice daily in two cohorts of HIV-1 infected patients failing their current ARV therapy due to the development of a RAL-resistant virus; 27 and 24 subjects were enrolled, with CD4+ T cell count <200 cells/μl and Centers for Disease Control and Prevention (CDC) Class C staging in 60%. The primary efficacy endpoint was the proportion of subjects on day 11 in whom the plasma HIV-1 RNA load decreased by ≥0.7 $\log_{10}$ copies/ml from baseline or was <400 copies/ml. VIKING participants in the first cohort began DTG 50 mg once daily for 10 days without other active drugs. After this period, the background regimens were optimized to include active drugs. A total of 78% of subjects achieved a viral load <400 copies/ml; the average decrease of HIV-1 RNA was 1.45 $\log_{10}$. The second VIKING cohort enrolled 24 subjects; after 10 days of DTG 50 mg twice daily, the background therapy was optimized including at least one active drug. The results showed that 96% of subjects in this second cohort had a viral load decrease to <400 copies/ml or a reduction of

at least 0.7 $\log_{10}$ from their baseline values. At week 24, 41% and 75% of subjects had an HIV-1 RNA load of <50 copies/ml in cohorts I and II, respectively. Further integrase genotypic evolution was uncommon. DTG had a good, similar safety profile with each dosing regimen. These data are the first clinical demonstration of the activity of DTG in subjects with HIV-1 resistant to RAL. Based on these findings, DTG 50 mg twice-daily dose has been chosen for the phase III trials in HIV-1 experienced INI-resistant subjects [Eron *et al.* 2013].

VIKING-3 was a multicenter, open-label, single-arm study assessing the antiviral activity and safety of DTG 50 mg twice daily for 24 weeks in 183 ARV-experienced adults with historical or current evidence of resistance to RAL or EVG, with a HIV-1 RNA level >500 copies/ml. After 7 days of open-label DTG, subjects received an optimized background therapy along with the study drug. At baseline, 124 patients had current resistance to INSTIs and 59 showed historical resistance to the class; median CD4+ T cell count was 140 cells/μl, 13 years of prior ARV therapy exposure, and CDC Class C staging in 56%, 79% had >2 N(t)RTI, 75% >1 NNRTI and 70% >2 PI resistance-associated mutations. Non-R5 tropic virus was detected in 61% of patients. HIV-1 RNA load declined by a mean of 1.4 $\log_{10}$ copies/ml at day 8, whereas the proportion of subjects with HIV-1 RNA <50 copies/ml at week 24 by FDA snapshot analysis was 63%. Virological response varied according to the genotype pathway of INSTI resistance. In subjects with Q148 pathway mutations, the virological response decreased with increasing number of secondary mutations. Overall background susceptibility score (number of active drugs in the optimized background therapy) was not associated with week 24 response. DTG 50 mg twice daily had a low (3%) discontinuation rate due to adverse events, similar to INSTI-naïve subjects receiving DTG 50 mg once daily. DTG 50 mg twice daily was shown to be highly effective in this heavy treatment-experienced population with INSTI-resistant virus [Castagna *et al.* 2014].

VIKING-4 was a phase III, randomized, double-blind, placebo-controlled, superiority study. A total of 30 ART-experienced adults, with a screening resistance to RAL/EVG and to two or more other ART classes, were randomized to DTG 50 mg twice daily or placebo, while continuing their failing regimen (without RAL/EVG) up to day 7. From day 8, all patients received open-label DTG with an optimized background regimen. The day 8 antiviral activity and safety/tolerability data were presented at the European AIDS Clinical Society (EACS) meeting held in Brussels, Belgium, on 16–19 October 2013. Patients enrolled in this study were highly ARV-experienced with a 17 years' prior median cART duration, comprising a median of 14 prior different cARTs. The proportion of Q148 viruses at baseline was higher in VIKING-4 DTG arm as well as plasma HIV-1 RNA load compared to those present in the placebo arm. The DTG activity reported was consistent with that observed in previous studies. The day 8 mean response was best for viruses without Q148 mutation: –1.43 $\log_{10}$ copies/ml (n = 5). Response for viruses with 'Q148 + 1' (9/14; 64%) was better than that in the VIKING-3 study (57/183; 31%). The DTG arm day 8 HIV-1 RNA mean change from baseline in subjects with 'Q148+ ≥2' mutations was lower (–0.9 $\log_{10}$ copies/ml). The most frequent adverse events were diarrhea, nausea and headache; five subjects developed a serious adverse event, all considered unrelated to study drug. Superior day 8 antiviral effect of DTG *versus* placebo confirms that antiviral activity was attributable to DTG and not to the failing regimen. DTG antiviral activity was consistent with the larger VIKING-3 pivotal phase III study results [Akil *et al.* 2013].

In all phase II and III trials, DTG has always demonstrated a favorable safety profile. Table 4 summarizes the more frequent adverse events reported. The majority of patients in each clinical trial experienced some adverse event during the course of treatment, with event rates ranging from 57 to 89%. Nausea, headache, diarrhea and sleep disturbances were among the most commonly reported adverse events, ranging from 5 to 23% of subjects. No dose-related patterns were identified. The majority of treatment-emergent adverse events were mild or moderate in nature. The frequencies of graded laboratory abnormalities were similar between all DTG treatment and comparator arms. Laboratory abnormalities reported in 1–5% of subjects included increased cholesterol, lipase, bilirubin, alanine aminotransferase/aspartate transaminase (ALT/AST), creatine phosphokinase (CPK) and prothrombin time, as well as decreased phosphorous and neutrophil count [Cottrell *et al.* 2013].

Data from SPRING-2, SINGLE and VIKING-3 were published in 2012 and data from SAILING

Table 4. Summary of adverse events reported in phase II/III clinical trials of dolutegravir.

Adverse event	SPRING-1: Composite DTG treatment groups, *n* = 155 (*n*, %)	SPRING-2: DTG arm, *n* = 411 (*n*, %)	SINGLE: DTG arm, *n* = 414 (*n*, %)	VIKING: cohorts I and II, DTG arm, *n* = 51 (*n*, %)	SAILING: DTG arm, III, *n* = 357 (*n*, %)	FLAMINGO: DTG arm, IIIb, *n* = 242 (*n*, %)
Nausea	19 (12)	59 (14)	59 (14)	NR	29 (8)	39 (16)
Headache	10 (6)	51 (12)	55 (13)	NR	33 (9)	37 (15)
Diarrhea	12 (8)	47 (11)	72 (17)	3 (6)	71 (20)	41 (17)
Nasopharyngitis	NR	46 (11)	62 (15)	NR	23 (6)	NR
Dizziness	5 (3)	23 (6)	37 (9)	NR	NR	NR
Sleep disturbances (insomnia, abnormal dreams, etc.)	3 (2)	21 (5)	94 (23)	3 (6)	NR	NR
Fatigue	5(3)	20 (5)	54 (13)	NR	15(4)	NR
Upper respiratory tract infection	NR	26 (6)	36 (9)	NR	38(11)	NR
Pyrexia	NR	20 (5)	NR	NR	NR	NR
Depression	NR	21 (5)	23 (6)	NR	NR	NR
Pharyngitis	NR	14 (3)	NR	NR	NR	NR
Bronchitis	NR	19 (5)	NR	3(6)	NR	NR
Anxiety	NR	14 (3)	14 (3)	NR	NR	NR
Cough	NR	NR	NR	3 (6)	33 (9)	NR
Rash	2 (1)	NR	14 (3)	NR	19 (5)	NR
Asthenia	4 (3)	NR	NR	NR	NR	NR

DTG, dolutegravir; NR, not reported.

were announced in 2013: these four studies formed the basis of the registration package leading to the FDA approval of DTG (Tivicay®) on 12 August 2013. With a similar registration package, DTG was approved in Europe on 21 January 2014 by the European Medicines Agency (EMA). The drug joins RAL and EVG as a guideline-preferred agent for the management of HIV-1 infected treatment-naïve patients [Shah *et al.* 2013].

Perspectives

Over the past 15 years, knowledge of cART side effects has improved and new, convenient, supposedly less toxic, and more tolerable molecules have become available, both in the oldest and in the new ARV classes. However, there is a need for simplified regimens that provide a lower pill burden, a reduced dose frequency and a more favorable safety profile, all combined with higher genetic barrier against viral resistance. Coformulated options, and even more, once-daily single tablet regimens represent the best cART simplification achieved so far. The first single pill once-daily option for HIV-1 therapy was approved in 2006 (TDF/FTC/EFV, Atripla®). The second one followed in 2011 (TDF/FTC/RPV, Complera®). Another single pill once-daily regimen (EVG/COBI/TDF/FTC, Stribild®) was recently approved by the FDA (20 August 2012) [Johnson and Saravolatz, 2014].

During the last years, INSTIs entered into clinical practice. Like the previously summarized issues, what is the role of INSTIs, and in particular that of DTG, in these scenarios?

There are now several INSTIs available for initial therapy of HIV-1 infected persons. All are potent and well tolerated, with favorable metabolic profiles. RAL and DTG have relatively fewer drug–drug interactions compared with EVG. Transmitted resistance to INSTIs is currently low. Resistance seems to be less common with DTG. All drugs belonging to the INSTI class share an impressive, rapid virus load decline in both treatment-naïve and experienced patients;

however, this characteristic does not seem to be associated with greater chance of long-term virological control when compared with other cART strategies, probably due to the relatively short period of use of INSTIs. DTG is the newest ARV drug and also the newest second-generation INSTI. The phase III clinical trials whose results are actually available compared DTG as first-line therapy in HIV-1 naïve subjects with the anchor drugs in the preferred regimens in each of the three classes. The SPRING-2 study was a double-blinded head-to-head comparison of DTG with RAL; the SINGLE study was a head-to-head double-blind study *versus* EFV; and the FLAMINGO study was an open-label head-to-head comparison with DRV/r. In all trials DTG has been always confirmed as not inferior (and sometimes superior) compared with the standards of care, both in terms of virological and immunological efficacy as well as in the safety profile.

Taken together, these studies suggest that once-daily 50 mg DTG, both in combination with either TDF/FTC or ABC/3TC and in the presence of HIV-1 RNA levels < or ≥ 100,000 copies/ml, is well tolerated and has sustained antiviral efficacy as initial therapy for the treatment of adults with HIV-1 infection. The drug is a valid alternative to the twice-daily RAL regimens. Furthermore, RAL and EVG regimens were not convenient since RAL required twice-daily dosing and EVG required food intake and pharmacological boosting. Studies in ARV-experienced patients, and in those harboring RAL/EVG resistant viruses, also show a high virological activity in this kind of challenging patient. In combination with up to two other ARV drugs, DTG was well tolerated with greater virological effects than RAL. All these findings may represent innovative changes in clinical practice and most likely in the near future may determine different approaches in the treatment of HIV-1 infected patients.

According with these studies, the main advantages of DTG are its safety and efficacy in both treatment-naïve and experienced patients, and its pharmacokinetic characteristics that allow once-daily administration independent from food, without boosting and with a low grade of drug–drug interactions. Furthermore, DTG exhibits an interesting resistance profile, probably due to the higher binding to the IN enzyme, when compared with RAL and EVG. As yet, in treatment-naïve patients we have not seen the emergence of resistance at virological failure, and the results of the VIKING studies confirm its high genetic barrier against RAL/EVG resistant virus, showing an impressive virological efficacy in the setting of ARV-experienced subjects. Some DTG disadvantages: it is not yet available as part of a fixed-dose combination and there is a creatinine effect with its use that should be monitored. DTG dosing, like COBI, is associated with a rise in serum creatinine of about 0.1–0.2 mg/dl in the first 2–4 weeks of treatment and tends to be stable over time. It is also due to inhibition of tubular secretion of creatinine, although the drug inhibits a different transporter than COBI. The overall effect however is similar. Pharmacokinetic studies and dose-ranging trials suggest DTG as a good candidate for a single-tablet regimen in a new coformulated pill. This possibility is actually under evaluation in a trial designed to explore the bioavailability of a fixed-dose pill containing DTG 50 mg/ABC 600 mg/3TC 300 mg [ClinicalTrials.gov identifier: NCT01366547].

The more rapid rate of viral attenuation seen with DTG may warrant consideration of this agent in clinical scenarios requiring rapid virological suppression, such as HIV-1 infected patients presenting with AIDS-defining illness or women presenting late in pregnancy. Furthermore, DTG characteristics make it a promising option in the treatment of HIV-1 infected organ transplant recipients [Waki and Sugawara, 2011]. The main aspects of a cART regimen in a HIV-1 infected transplant recipient should meet at least the following requirements: be potent with a high resistance barrier; have low toxicity profile and lack of interactions with immunosuppressive agents; no (or low) impact on graft function; and, finally, an easy dosing. DTG responds to all these conditions [Fantauzzi *et al.* 2013].

With the availability of DTG in anti-HIV-1 management, new cART strategies may require to be explored with 'ad hoc' trials to address several emerging issues. What is the potential for potent, tolerable and safe combination ARV regimens that do not need the inclusion of N(t)RTIs or pharmacokinetic boosting with RTV or COBI? Could dual combination therapies such as INSTIs (RAL or DTG) and NNRTIs or PIs, or other dual strategies, offer an effective, safe and durable alternative at the current ARV regimens? Several dual ARV combinations have been studied or are actually under investigation (i.e. LPV/r + RAL, boosted PIs + 3TC, DRV/r + RAL,

DRV/r + ETR, DTG + RPV, etc.) in different clinical settings – as first-line or simplification/maintenance strategies as well as rescue approaches in multi-experienced patients. The results of these trials will probably change in the near future the therapeutic approach to HIV-1infected persons [Burgos *et al*. 2012; Calin *et al*. 2012; Di Giambenedetto *et al*. 2013; Katlama *et al*. 2010; Reynes *et al*. 2013]. With its high barrier to resistance, as emerged in the VIKING studies, in which DTG functional monotherapy acted as did DRV/r in the POWER trials [Clotet *et al*. 2007], what about DTG monotherapy? DTG has the potential to have a major effect in low-income and middle-income countries, where most HIV-1 infections exist. In these settings, the World Health Organization (WHO) now recommends for naïve patients a preferred single-tablet cART with EFV/TDF/3TC [WHO, 2013]. ARV combinations with newer drugs conferring proven efficacy at lower doses might provide not only attractive and more affordable alternatives but also greater tolerability and safety.

New ARV therapeutic strategies are in development. In this perspective, long-acting ARV drugs may improve adherence and extend opportunities for therapeutic or prophylactic interventions in different patient populations. Investigational long-acting injectable nanoformulations of RPV and GSK1265744 (a long-acting DTG analogue) are clinical stage development candidates. At present, phase I studies of the pharmacokinetics and safety of each long-acting formulations, alone and in combination, indicate that a monthly dosing regimen is possible for HIV-1 treatment. An ongoing phase IIb trial of oral GSK1265744 and oral RPV is evaluating this two-drug regimen for maintenance of virological suppression. Moreover, additional preclinical and clinical trials indicate a potential use of each agent for HIV-1 pre-exposure prophylaxis [Spreen *et al*. 2013].

In conclusion, DTG represents an interesting molecule, with the potential to improve the adherence of HIV-1 infected patients and increase the long-term tolerability of cART. With its potent activity, tolerability, ease of dosing and minimal drug interaction profile, DTG is poised to become one of the key components in the treatment of HIV-1 infection.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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