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REVIEW

Dolutegravir, Second Generation Integrase Inhibitor: A New Hope for HIV Patient

Geeta Yadav*, Piyush Kumar†, Yugal Kumar‡ and Pradeep Kumar Singh‡

Undeterred efforts are reported and still continue in future to achieve the goals of virologic suppression in HIV-infected individuals. Dolutegravir is the result of all the efforts made in this direction. It is a recent integrase inhibitor drug approved by the US FDA (Food and Drug Administration) for use in the treatment-naïve and treatment-experienced HIV-infected patients. This article has reviewed all the aspects of the drug, including the structural and functional analyses, *in vitro* activity, pharmacokinetics, drug-drug interactions, MOA, metabolism, excretion, dosing/adverse effects and resistance profile. Dolutegravir is a potent and well tolerated antiretroviral agent that can play an important role in the treating patients harboring resistance to other antiretrovirals. Some new combinations of drug with other antiretrovirals are also in the pipeline that can increase the immunologic response of the HIV patients.

Keywords: Dolutegravir; Antiretroviral; Integrase inhibitor; Human Immunodeficiency Virus (HIV)

1. Introduction

Undoubtedly with the use of antiretroviral drugs of high potency, tolerability, and resistance profiles, lifespan time has increased in HIV patients. However, even after so much advancement in therapy, patients are struggling with an unknown, fear of death (Serrao et al. 2009; Hawkins 2010). Therefore, the need for new antiretroviral agents is still substantial even after more than 20 years into the era of antiretroviral therapy. Present antiretroviral drugs have a better tolerability profile, higher barriers to resistance, and less drug–drug interactions. These principles have inspired the scientists all over the world to develop new agents that are mainly focused on novel therapeutic targets. The drugs targeting on critical steps in the life cycle of HIV-1 include HIV-1 reverse-transcriptase inhibitors (both nucleoside analogue and non-nucleoside inhibitors), HIV-1 protease inhibitors and HIV-1 entry inhibitors (fusion inhibitors and CCR5 antagonists). The newest approved class of drug in HIV treatment is the integrase inhibitor (INI).

Retroviral DNA integration with the host DNA is a crucial step in the life cycle of human immunodeficiency virus (HIV) (Sakai et al. 1993), as shown in **Figure 1**. This integration process is a multistep process initiated by the viral integrase (IN) enzyme for the insertion of the viral DNA into the host genome. The process of HIV-1 integration occurs through 3 essential steps: formation of the preintegration viral DNA complex, 3′ processing and strand transfer (Asante-Appiah & Skalka 1997). HIV IN binds at specific sequences in the long terminal repeats (LTRs) of the viral DNA. This DNA binding process takes place in the cytoplasm. The next step is cutting of GT dinucleotides from the 3′ termini of the linear cDNA through a process called 3′ processing. The next step is translocation of processed viral DNA into the nucleus, where IN inserts the viral DNA into the host chromosome by a process called strand transfer which is a part of the preintegration complex (Asante-Appiah & Skalka 1997; Engelman, Mizuuchi & Craigie 1991).

Integrase inhibitors (INIs) represent a class of drug used in the treatment of HIV infected people, blocking the HIV genome transfer and integration into the host cell DNA (Powderly 2010). Raltegravir (RAL), first drug of this category which got FDA approval. It is highly convincing drug in treating antiretroviral-naive and experienced subjects and a recent addition is elvitegravir (EVG) (Markowitz et al. 2007; Steigbigel et al. 2008; Mbisa, Martin & Cane 2011; DeJesus et al. 2006; Zolopa et al. 2010). But these first-generation INIs also suffer from some severe drawbacks like they share some common resistance pathways noticed during clinical studies of RAL. Infected subjects found to have virus with 1 of 3 signature mutational pathways like N155H, Q148H/K/R, or Y143C/H/R, in the integrase enzyme gene (Cooper et

* Department of Pharmaceutical Sciences, Manav Bharti University, Solan, IN

† Department of Chemistry, Indian Institute of Technology, Kanpur, Uttar Pradesh, IN

‡ Department of Computer Science and Engineering, Jaypee University of Information Technology, Waknaghat, Solan, IN

Corresponding author: Geeta Yadav (yadavgeeta172@gmail.com)

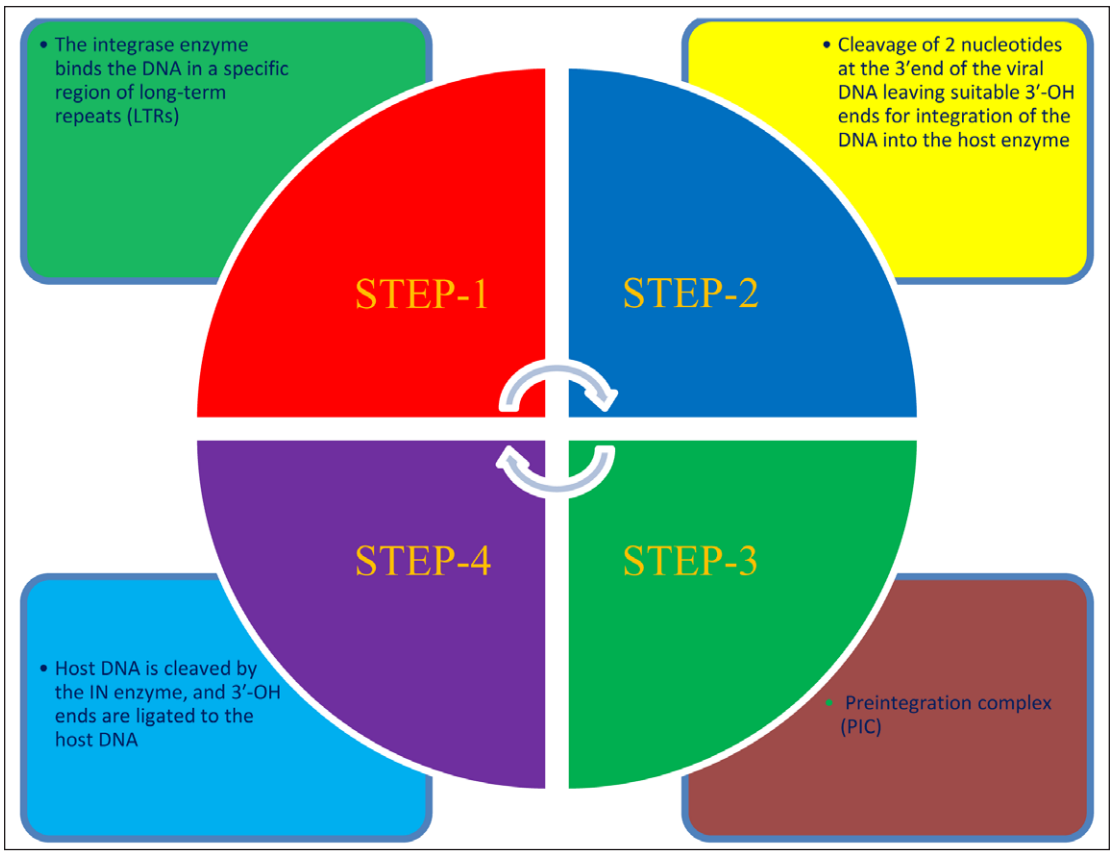

Figure 1: Schematic representation of HIV integration.
Abbreviations: LTRs, long-term repeats; PIC, preintegration complex.

al. 2008). So, in these circumstances continuing RAL treatment may lead to some secondary mutations (Y143 or Q148 pathways) evaluation (DeJesus et al. 2007). In addition to this, EVG does not have any activity against RAL-resistant isolates and same case is with RAL (DeJesus et al. 2007; Marinello et al. 2008; Garrido et al. 2012). Therefore, there is a need for new INIs with a high genetic barrier to resistance as well as high anti-HIV activity. So, recent drug to fulfill all these basic requirements is Dolutegravir (DTG). This review article aims to cover all the aspects related to the dolutegravir which will help the scientists, academicians and common men to satisfy their knowledge pangs, like *in vitro* activity, pharmacokinetics, drug-drug interactions, MOA, metabolism, excretion, dosing/adverse effects and resistance profile of dolutegravir. **Figure 2** explains methodology and evaluation of dolutegravir with the help of different information sources.

Dolutegravir (DTG) discovered by Shionogi and GlaxoSmithKline research collaboration, is a second generation novel HIV-1 integrase strand transfer inhibitor having activity against INI resistant viruses as well as favorable pharmacokinetic properties (Sato et al. 2009; Underwood et al. 2009). It is generally recommended in combination with other antiretroviral agents. It is marketed as a small, yellow, 50-mg tablet and can be consumed without any regard to time and food.

There are excellent reviews and research papers recently published which sum up the side effects and other clinical phase studies of Dolutegravir in combination with other drugs (Hoffmann et al. 2017; Sax et al. 2017).

2. Different Aspects of Dolutegravir Drug

2.1. Structural and functional analyses of Dolutegravir (DTG)

Dolutegravir (DTG, S/GSK1349572) effectively inhibits HIV-1 IN variants which are resistant to the first-generation INIs. Potency of DTG is mainly attributable to its structure which shares almost the same space within the IN active site as other INIs. DTG also makes strong interactions with the β4-α2 loop of the catalytic core domain. Dolutegravir molecular structure has three main structural parts like tricyclic metal-chelating core, difluorophenyl ring and linker group as shown in **Figure 3**. Tricyclic metal-chelating core binds to the intasome active site with three coplanar oxygen atoms coordinated to Mg^{2+} cations. The extended linker region of DTG allows it to enter farther, deeper into the pocket as vacated by the displaced viral DNA base, to make more compatible bonding with the viral DNA (Hare et al. 2011).

2.2. In vitro *activity*

Dolutegravir has shown potent *in vitro* activity against many INI-resistant mutants as well as against wild-type HIV-1. It has shown potent *in vitro* activity against HIV-1 with mean EC_{50} of 0.5 nM to 2.1 nM, IC_{50} of 2.7 nM and an IC_{50} of 2.0 nM in peripheral blood mononuclear cells (PBMC) and MT-4 cells. The drug also shows activ-

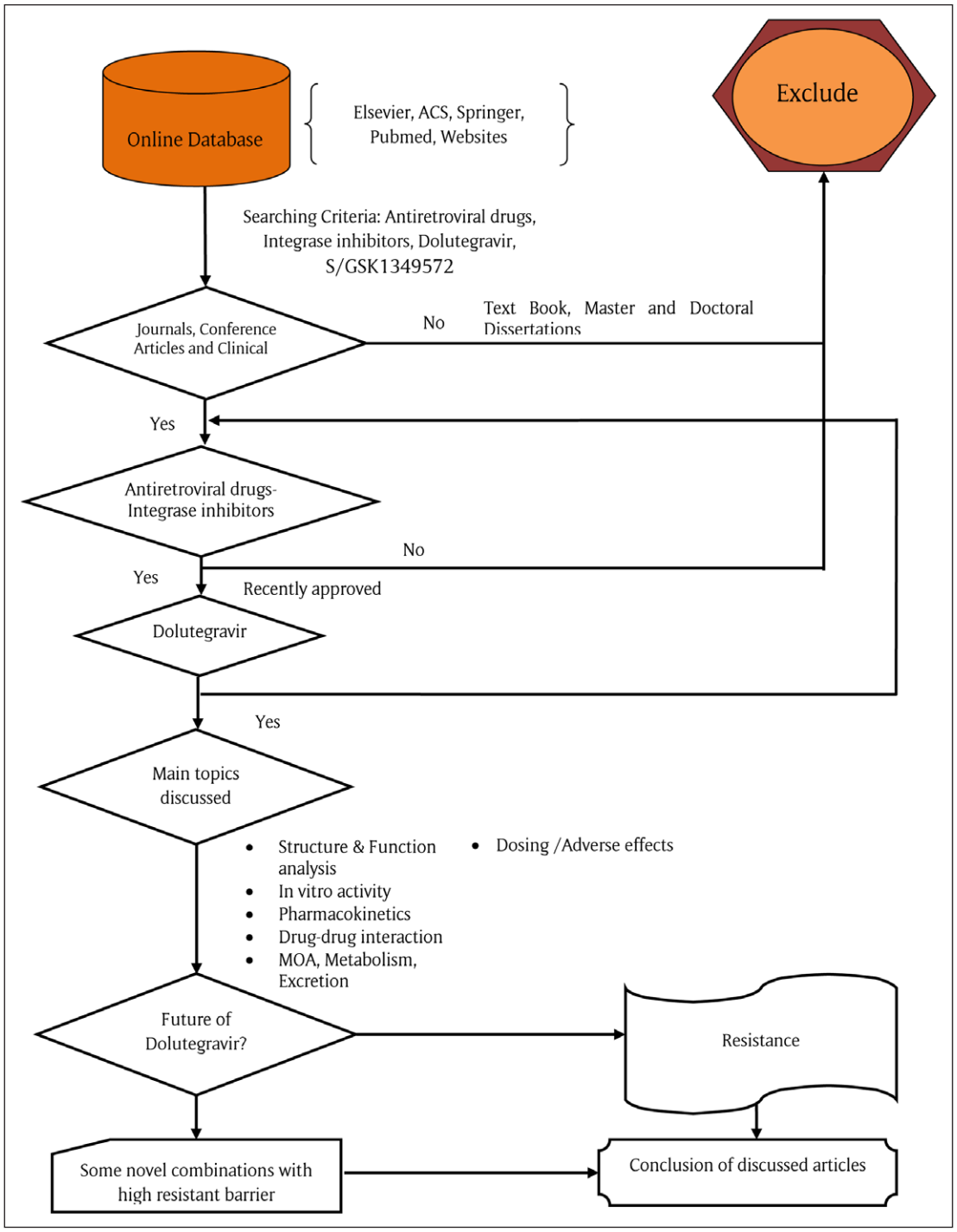

Figure 2: Methodology and Evaluation of review on Dolutegravir.

ity against HIV-2 viruses (EC_{50} of 0.09 nM to 0.61 nM) in PBMC assays. Cellular toxicity value is in the micromolar range in variant cells, which indicates that the antiviral effect of S/GSK1349572 is not due to cytotoxicity. S/GSK1349572 shows potency against all integrase resistant single mutants with an FC as high as 3.6-fold. 32 nM or higher concentrations of S/GSK1349572 reported not a single virus with high resistance. *In vitro* experimental studies have shown no toxicity when used with other antiretrovirals, but found a synergistic effect with nevirapine, efavirenz, abacavir, stavudine, lopinavir, amprenavir and enfuvirtide drugs and an additive effect with maraviroc. Results indicated no effect on efficacy on exposure to the adefovir and ribavirin (Kobayashi et al. 2011).

2.3. Pharmacokinetics

Dolutegravir has a favourable pharmacokinetic profile with terminal half-life of approximately 13–15 h (Min et al. 2010; Min et al. 2011). AUC_{0-24h} and C_{max} values are slightly less than the dose in the range of 2–50 mg following single and multiple doses. One notable change is the nonlinearness in C_{max} and AUC with the increase in dose. So, phase 3 clinical trial selected a twice-daily 50 mg dose instead of a once-daily 100 mg dose (Min et al. 2011; Patel, Song and Borland 2012; Song et al. 2012). Dosing interval (Ctau) for a 50 mg dose reported 1.6 μg/ml as the geometric mean steady-state concentration, which is about 25-fold higher than the protein-adjusted IC_{90} (0.064 μg/ml). A monotherapy study of, 10 days of dolutegravir 50

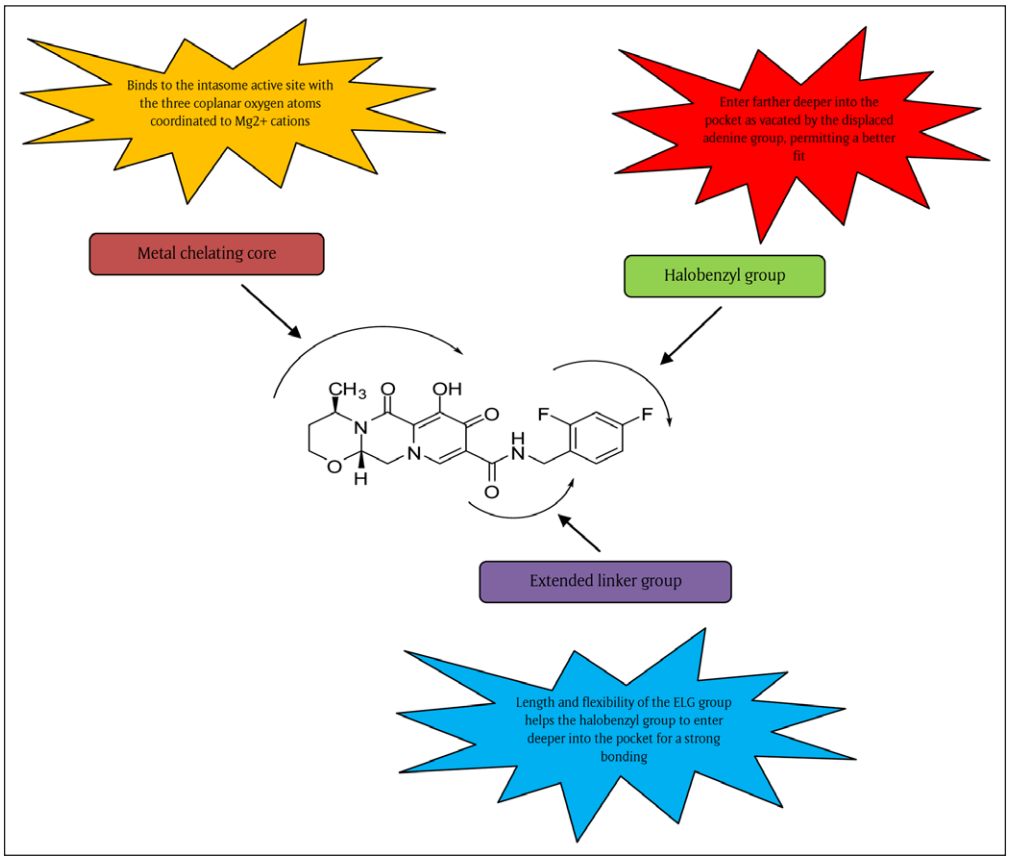

Figure 3: Structural and functional analysis of Dolutegravir.

Table 1: Dolutegravir (DTG) drug interaction with integrase inhibitors and other category drugs.

S.No	Interacting drug class	Interacting drug	Effect on dolutegravir
1	Antiretrovirals NRTIs	Tenofovir	No significant effect observed (Song et al. 2010)
2	Antiretrovirals NNRTIs	Efavirenz	DTG AUC, C_{max}, and C_{min} decreased 57, 39, and 75% (Song et al. 2011)
		Etravirine	DTG AUC, C_{max}, and C_{min} decreased 70.6, 51.6, and 87.9%. (Song et al. 2011) ETR/DRV/r administration results in 25, 11.8, and 37.1% decrease in DTG AUC, C_{max}, and C_{min} ETR/LPV/r administration results in 11, 7, and 28% increase in DTG AUC, C_{max}, and C_{min} (Song et al. 2011)
3	Antiretrovirals PIs	Darunavir/r	DTG AUC, C_{max}, and C_{min} decreased 22, 11, and 38% (Song et al. 2011)
		Atazanavir	DTG AUC, C_{max}, and C_{min} increased 91, 50, and 180% (Song et al. 2011)
		Lopinavir/r	No significant effect observed (Song et al. 2011)
		Fosamprenavir	DTG AUC, C_{max}, and C_{min} decreased 35, 24, and 49% (Song et al. 2014)
		Tipranavir	DTG AUC, C_{max}, and C_{min} decreased 59, 46, and 76% (Song et al. 2011)
4	Antituberculosis drugs	Rifampin	DTG AUC and C_{min} increased 33 and 22% with DTG 50 mg b.i.d.+ rifampin 600 mg q.d. compared with DTG 50 mg daily (Dooley et al. 2013)
		Rifabutin	DTG AUC and C_{min} decreased 5 and 30%, C_{max} increased 15% (Dooley et al. 2012)
5	Acid-reducing agents-PPIs/H2 RA	Omeprazole	No significant effect observed (Patel et al. 2011)
		Antacids	DTG AUC, C_{max}, and C_{min} decreased 73.6, 72.4, and 74.4% (Patel et al. 2011)

DTG, Dolutegravir; ETR, Etravirine; EVG, Elvitegravir; LPV, Lopinavir; NNRTI, Non-nucleoside reverse transcriptase inhibitor; NRTI, Nucleos(t)ide reverse transcriptase inhibitor; PI, Protease Inhibitor; PPI, Proton pump inhibitor; r, Ritonavir; RAL, Raltegravir; AUC, Area under the Curve; Cmax, Maximum concentration; Cmin, Minimum concentration, LPV, Lopinavir; DRV, Darunavir; ETR, Etravirine.

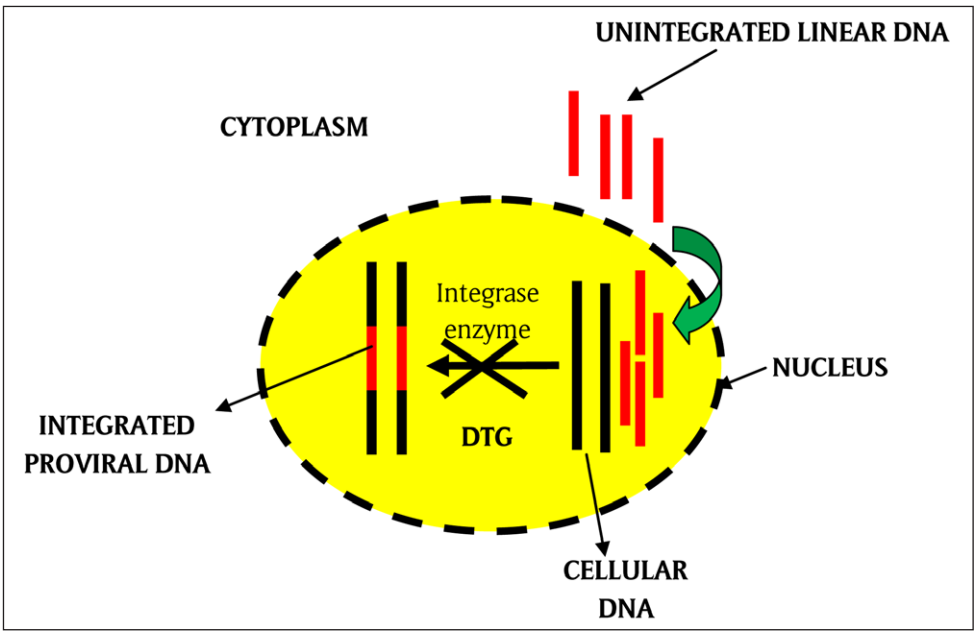

Figure 4: Mechanism of action of DTG.

mg daily dose in integrase inhibitor naïve HIV-1-infected subjects demonstrated a reduction in HIV-1 RNA. This reduction sustained for 4 days after discontinuation of dolutegravir only because of plasma concentrations which remained above the protein adjusted IC_{90}. Variability in exposure was minimum like 50 mg dosing is achieved a geometric mean C_{max} of 3.34 mg/ml (16% coefficient of variation), an AUC_{0-24h} of 43.4 mg/ml (20% coefficient of variation), a $t_{1/2}$ of 12.0 h (22% coefficient of variation) and a C_{24h} of 0.83 mg/ml (26% coefficient of variation) (Min et al. 2011; Patel, Song and Borland 2012; Song et al. 2012). According to reports, a pediatric granule formulation of dolutegravir is currently under development phase and preliminary data investigation also reported the increased exposure of granules when mixed with purified water in comparison to the tablet formulation (Patel, Song and Borland 2012).

2.4. Drug–drug interactions

The dolutegravir pharmacokinetic study evaluated the effect of food on its absorption according to fat content. (Song et al. 2012). Fat content affects the absorption of dolutegravir as noticed by the increased median T_{max} from 2h to 5h for low, moderate and high-fat meals respectively. Whereas dolutegravir AUC increases from 33 to 66% when administered with low-fat (300 kcal, 7% fat), moderate fat (600 kcal, 30% fat) and high fat food (870 kcal, 53% fat), respectively (Min et al. 2011; Song et al. 2012). But these changes are not expected to affect safety or efficacy. Dolutegravir can be prescribed without any regard to food. Dolutegravir causes drug-drug interactions with integrase inhibitors and some other drugs as shown in **Table 1**.

2.5. Mechanism of Action

Dolutegravir inhibits HIV integrase enzyme by binding to specific amino acids in the active site and block the strand transfer step which results in no formation of integrated proviral DNA, which is essential for the HIV replication cycle as demonstrated in **Figure 4**. In this process, the integrase inhibitor chelates with two Mg^{2+} ions in the integrase catalytic active site and unable the integrase enzyme to complete the strand transfer (Min et al. 2010). Accumulation of 2-long terminal repeat (2-LTR) circles in treated cells indicate the integrase strand transfer reaction inhibition by less DTG concentration in comparison to that causes cell toxicity (Bar-Magen et al. 2009; Sloan & Wainberg 2011).

2.6. Metabolism/Excretion

Dolutegravir metabolism follows a major pathway CYP3A4 (UGT1A1 glucuronidation) and two minor pathways (UGT1A3 and UGT1A9) catalyse by UDP-glucuronosyl transferase (UGT) 1A1 enzyme as shown in **Figure 5**. *In vitro studies* report DTG as neither a cytochrome P_{450} inducer nor an inhibitor. However, dolutegravir is a OCT2 inhibitor (Song, Borland & Chen 2012). Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp (ULC, V.H., 2013). It is the predominant circulating compound in plasma and the renal elimination of unchanged drug is extremely low (<1% of the dose). Recovery rate of DTG in feces and urine is approximately 53% and 31% of a dose respectively, primarily as DTG-glucuronide and other minor metabolites (Castellino et al. 2013).

2.7. Dose/Adverse effects

Dolutegravir tablets are usually taken unboosted, orally and without regard to food (Quashie, Sloan & Wainberg 2012). Different dose combination studies with other drugs performed to find the best combination with high resistance barrier as shown in **Table 2**. Dolutegravir Phase III SPRING-2 trial study showed common adverse effects like nausea, headache, diarrhea, nasophryngitis and also a slight increase in creatinine level due to inhibition of creatinine secretion. However, it has no effect on glomerular filtration rate (Raffi et al. 2012; Walmsley et al.

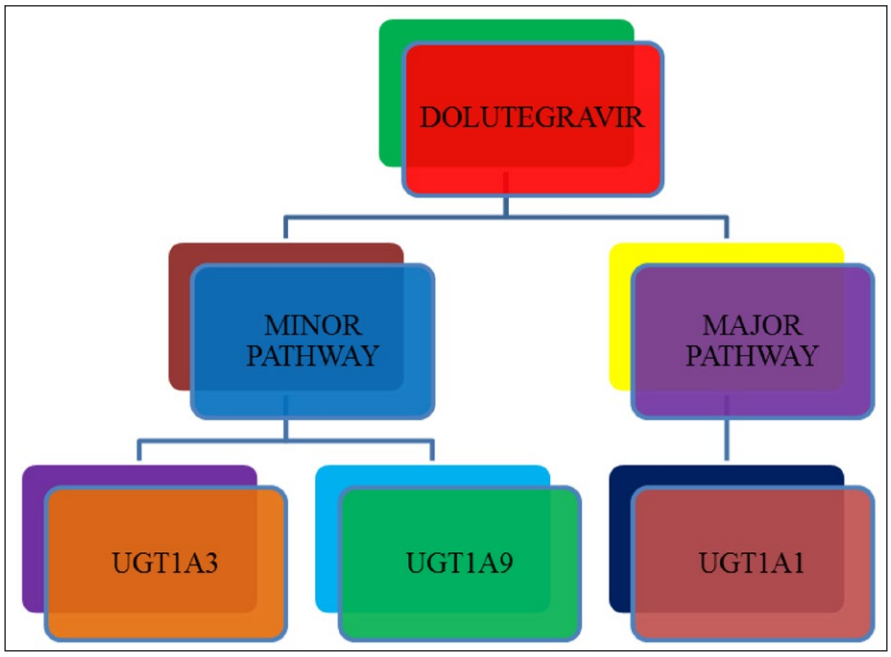

Figure 5: Metabolic pathway of dolutegravir.

Table 2: Dolutegravir (DTG) drug combinations in different phases of the clinical trials.

S.No	Phase study	Patients	Dolutegravir vs other drug combinatons
1	Phase III SPRING-2 Study	Treatment naïve	Dolutegravir 50 mg once daily versus raltegravir 400 mg twice daily, each in combination with either tenofovir DF/emtricitabine (Truvada) or abacavir/lamivudine (Epzicom) (Song et al. 2012)
2	Phase III SINGLE Study	Treatment naïve	Dolutegravir 50 mg in combination with abacavir/lamivudine (Epzicom) once daily versus tenofovir DF/emtricitabine/efavirenz (Atripla) once daily (https://clinicaltrials.gov/ct2/show/NCT01227824)
3	Phase III SAILING Study	Treatment experienced, integrase inhibitor-naïve	Dolutegravir 50 mg once daily versus raltegravir 400 mg twice daily, each in combination with background therapy (https://clinicaltrials.gov/ct2/show/NCT01263015)
4	Phase III VIKING-3 Study	Treatment-experienced with previous or current failure on raltegravir or elvitegravir	Open-label dolutegravir 50 mg twice daily with current failing background regimen for 7 days, then with an optimized background regimen (https://clinicaltrials.gov/ct2/show/NCT01231516)
5	Phase III VIKING-4 Study	Treatment-experienced with virus resistant to raltegravir and/or elvitegravir at screening	Dolutegravir 50 mg twice daily versus placebo, each in combination with current failing background regimen for 7 days, then with open-label dolutegravir 50 mg twice daily in combination with an optimized background regimen for both arms (https://clinicaltrials.gov/ct2/show/NCT01328041)
6	Combination under study		A fixed-dose combination (FDC) tablet (dolutegravir 50 mg abacavir 600 mg/lamivudine 300 mg) and a dolutegravir pediatric granule (https://clinicaltrials.gov/ct2/show/NCT01568892; https://clinicaltrials.gov/ct2/show/NCT01366547)

2012). Some common drug -related adverse events such as diarrhea, nausea, and headache also notified during Phase III VIKING-3 trial in treatment-experienced subjects (Walmsley et al. 2012).

2.8. Resistance

Dolutegravir (DTG) found to show a higher genetic barrier to resistance than raltegravir and elvitegravir (Tang & Shafer 2012). As such resistance mutations associated with dolutegravir have not yet been identified, but viruses containing G140S, E138K, R148H, R263K, and G140S/Q148HRK mutations have been found to show some level of resistance to dolutegravir (Tang & Shafer 2012; Quashie, Sloan & Wainberg 2012). Raltegravir-resistant virus carries a number of mutations, among which a mutation at position Q148 had more reduced susceptibility to dolutegravir (Underwood et al. 2012). *In vitro* selection studies reported R263K mutation which commonly emerges in integrase in the presence of dolutegravir. R263K confers low-level resistance against dolutegravir

and diminishes HIV DNA integration and viral fitness. As well as no secondary mutation H51Y and E138K has been found to compensate for the defects associated with the R263K primary resistance mutation against dolutegravir. All secondary mutations have a modest effect on resistance against this drug (Mesplède et al. 2013; Quashie et al. 2012).

3. Future of Dolutegravir

ViiV Healthcare has requested US regulatory for the approval of a new single-tablet regimen (STR), a combination of dolutegravir, lamivudine and abacavir drugs. According to the company reports, a European regulatory application has also been submitted. In the aforementioned trials this combination worked well as separate pills. So, If approved, this new formulation would give the first single-pill, once-daily regimen that does not contain tenofovir/emtricitabine and but could be beneficial especially for people suffering from kidney disease or osteoporosis. Results presented at Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), also proved the statistical superiority of dolutegravir over darunavir/ritonavir. Based on these findings the researchers conclude that a single pill of dolutegravir may provide a new option for first-line HIV treatment (Boyd & Cooper 2013).

4. Conclusion

HIV-1 integrase enzyme is a unique target for antiretroviral therapy. Dolutegravir, a once-daily HIV strand integrase inhibitor currently approved for HIV-1 infected patients, provides equivalent antiviral efficacy and better tolerability in comparison to the already approved antiretroviral drugs. Incessant efforts are going on for the approval of new single-tablet regimen (STR) containing dolutegravir, abacavir and lamivudine and also it would reduce the number of pills required for effective antiretroviral treatment. Because of its unique mechanism of action, demonstrated virologic activity, resistance profile and tolerability, it is a significant advancement in HIV-1 therapeutics which will help HIV patients in the long run.

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Competing Interests

The authors have no competing interests to declare.

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