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# Dolutegravir: Background, Pharmacokinetics, Adverse Drug Reactions, Drug Interactions, Pregnancy and Breast-Feeding Profile

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## Abstract

Integrase strand transfer inhibitors represent a novel class of antiretroviral drugs designed to obviate the action of the viral integrase enzyme, which is responsible for insertion of the viral genome into the host cellular deoxyribonucleic acid. Dolutegravir has got great affinity for plasma proteins, and 99% of dolutegravir is attached to plasma proteins, and it is independent of the plasma concentration. Dolutegravir has better penetration to distinctive body compartments and seems to cross the blood–brain barrier. Dolutegravir is revealed for use in combination with distinctive antiretroviral agents for the management of Human Immunodeficiency virus-1 infection in adults and adolescents twelve years and older weighing at least forty kilograms. Dolutegravir is an integrase strand transfer inhibitor that functions by suppressing the interjection of Human Immunodeficiency (HIV) virus deoxyribonucleic acid into host cells, thereby obviating subsequent viral duplication. Adverse drug reactions observed consummate ubiquitously in clinical trials, involving dolutegravir 50 mg once daily in the management regimen, were nausea, diarrhoea, headache, fatigue, asthenia, nasopharyngitis, insomnia, dizziness, abnormal dreams, pyrexia, and depression. The co-administration of dolutegravir and rifampicin consequently leads to a reduction of dolutegravir levels in the blood. Two folding the required daily dose of dolutegravir is recommended for appropriate clinical efficacy.

**Keywords:** Breast Feeding; Adverse Drug Reactions; Dolutegravir; Drug Interactions; Pharmacokinetics

## Introduction

According to the latest antiretroviral therapy (ART) clinical guidelines, the Efavirenz-based regimen has been replaced by the Dolutegravir (DTG)-based regimen due to its favourable profile of maintained viral suppression and immunological recovery [1]. The recommended regimen for the primary management of HIV is Tenofovir (TDF) + Lamivudine (3TC) + Dolutegravir (DTG) also known as TLD. DTG is cheap, has an increased genetic barrier to resistance, and is accessible as a fixed-combination pill, and hence was

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introduced as the preferred 1st-line therapy for HIV by the WHO in 2018 [2]. Dolutegravir (GSK1349572) is a potent inhibitor of the HIV-1 integrase that has shown good safety, tolerability, predictable pharmacokinetics and efficacy in treatment naïve and experienced adults in Phase III trials. Dolutegravir is nowadays FDA and EMA confirmed for both adults and adolescents twelve years and older, weighing ≥ 40 kg, at a dose of 50 mg once a day depending in part on the data observed herein [3, 4]. Dolutegravir (DTG) is increasingly being used in admixture with nucleoside/nucleotide reverse transcriptase inhibitors. Currently, the WHO has released new antiretroviral (ART) management guidelines recommending DTG-based management as the preferred 1st-line management alternative for all adults, adolescents, and children, involving women and adolescent girls who have access to identical and reliable contraception [5]. DTG is well tolerated and hastily prevents viral replication [6, 7]. Dolutegravir sodium is a second-generation HIV integrase strand transfer inhibitor (INSTI) and it belongs to BCS class II drug, describing that it is a meagrely soluble and a highly permeable drug, formulated pro-liposomes to accelerate the oral bioavailability of the drug using lipids and carriers [8]. Dolutegravir is an HIV INSTI that has been confirmed for the treatment of HIV infection in adult and paediatric (12 years and older) patients who are management-naive, management-experienced but INSTI naive, and management-experienced and INSTI-resistant. Studies in healthy subjects observe that dolutegravir is well tolerated, has mild to marked pharmacokinetic variability, and achieves therapeutic concentrations with once-daily dosing without the need for pharmacokinetic boosting [9, 10]. The 2nd-generation HIV-1 integrase strand transfer inhibitor (InSTI) dolutegravir (DTG) has had sudden diagnosable symptoms impact, observing both efficacy and a great obstacle to resistance. Despite the noticeable success of DTG, its pharmacodynamic properties are deficiently understood. The clinical efficacy of antiretroviral medicines based on multiple factors. The further essential is constitutive antiviral activity, which is a work of both the IC50 and the dose-response curve slope in all pharmacodynamic models. However often overlooked, slope is a significant magnitude of efficacy because of its exponential relationship with suppression. Great slopes for HIV-1 protease inhibitors and allosteric integrase inhibitors (ALLINIs) reflect inhibition at many steps in the viral life cycle. The first-generation InSTI raltegravir has not revealed activity at HIV-1 life cycle steps distinctive than integration, but DTG has not been attested for such activity [11, 12].

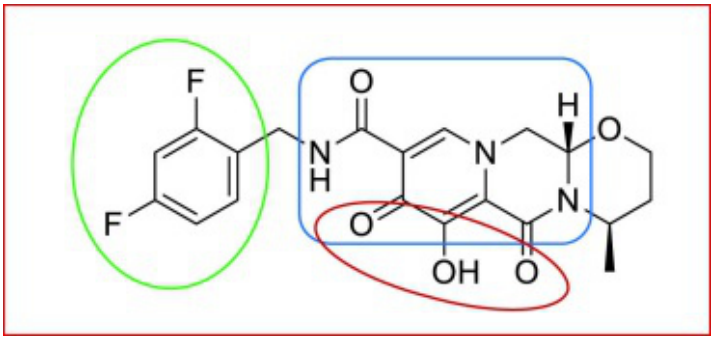


Figure 1 structures of dolutegravir. Red ovals encircle the oxygen atoms that chelate the divalent metal cations in the active site; green ovals encircle the halo benzyl groups; and blue boxes encircle the approximate regions of the scaffolds that can accommodate positive charge after chelation of the metals.

**Pharmacokinetics:** Dolutegravir has a suitable pharmacokinetic profile with terminal $t1/_2$ of approximately 13–15 hr. Area under curve 0–24hr and Cmax values are slightly less than the dose in the range of 2–50 mg following single and multiple doses. A monotherapy study of, 10 days of dolutegravir 50 mg daily dose in integrase inhibitor naïve HIV-1-infected subjects demonstrated a reduction in HIV-1 RNA. This decrement sustained for four days after discontinuation of dolutegravir only because of plasma concentrations which remained above the protein adjusted IC90. Variability in liability was minimum like 50 mg dosing is reached a geometric mean C-max of 3.34 mg/ml (16% coefficient of variation), an AUC 0–24hr of 43.4 mg/ml (20% coefficient of variation), a t1/2 of 12.0 hr (22% measurable of variation) and a C24hr of 0.83 mg/ml (26% measurable of variation) [13]. Absorption: Dolutegravir is hastily absorbed pursuing oral administration. The median maximum plasma concentration is reached 1.5–2.5 hours after oral uptake with a mean $t1/_2$ of 12–15 hours, delivering feasible for once-daily dosing without the seek for pharmacological boosting. Bioavailability varies with fat content [14]. Distribution: Dolutegravir has got great affinity for

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plasma proteins, and 99% of dolutegravir is attached to plasma proteins, and it is independent of the plasma concentration. Dolutegravir has good penetration to distinctive body compartments and seems to cross the BBB [15]. Metabolism/Excretion: Dolutegravir metabolism follows a preponderance pathway CYP3A4 (UGT1A1 glucuronidation) and two minor pathways (UGT1A3 and UGT1A9) catalyse by UDP-glucuronosyl transferase (UGT) 1A1 enzyme. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp. It is the paramount circulating constituent in plasma and the renal elimination of unchanged drug is extremely low (<1% of the dose). Recovery rate of DTG in faeces and urine is approximately 53% and 31% of a dose respectively, initially as DTG-glucuronide and distinctive minor metabolites [13]. Elimination: The terminal t1/2 is about 14 hours. The apparent oral clearance is near 1 liter/hour. Fifty three percent of the total oral dose of dolutegravir is excreted unchanged in the faeces, thirty two percent through urine as glucuronide (eighteen percent) or alkylated product (three-point five percent), and distinctive organic conjugated products sequencing from phase II liver metabolisms. About 1% of unchanged dolutegravir is excreted through urine, rendering it relatively safer to use in mild or moderate renal impairment [16].

**Indications:** Dolutegravir is described for usage in conflation with distinctive antiretroviral agents for the management of HIV-1 infection in adults and adolescents twelve years and older weighing at least forty kilograms. Genotype testing may be applicable for patients experiencing virologic failure during antiretroviral treatment. Meager virologic reactions was reported in patients with an INSTI resistance Q148 replacement plus 2 or further another INSTI-resistance replacement, enclosing L741/M, E138A/D/ K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R [17]. Mechanism of action of dolutegravir: Dolutegravir functions by interposing with an enzyme necessitated by HIV called integrase. Using Dolutegravir as section of combination therapy downgrades HIV's capability to infect cells and create copies of itself.

Dolutegravir is an INSTI that functions by suppressing the interjection of HIV deoxyribonucleic acid (DNA) into host cells, thereby obviating subsequent viral duplication. It fits loosely into the attaching pocket of the intasome and undergoes conformational revamps in the pocket structure while retaining its attaching capability [18, 19].

**Adverse drug reactions:** Adverse events observed consummate ubiquitously in clinical trials, involving dolutegravir 50 mg once daily in the management regimen, were nausea, diarrhoea, headache, fatigue, asthenia, nasopharyngitis, insomnia, dizziness, unusual dreams, pyrexia, and depression. Ubiquitous laboratory deformities enclosed enhanced alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol and lipase, and hyperglycaemia. Adverse events have occurred with similar frequency in dolutegravir and raltegravir treatment groups. Adverse events observed in dolutegravir-treated children have been similar to those reported in adults [17, 20-23]. Dolutegravir tablets are often taken un-boosted, orally and without food. Dolutegravir Phase III SPRING-2 trial survey revealed consummate adverse drug reactions like nausea, headache, diarrhoea, nasopharyngitis and also a slight elevates in creatinine level due to inhibition of creatinine secretion. However, it has no effect on glomerular filtration rate. Some common drug -related adverse events such as diarrhoea, nausea, and headache also notified during Phase III VIKING-3 trial in treatment-experienced subjects [13]. There is more evidence that the risks of weight gain, insomnia, immune reconstitution inflammatory syndrome (IRIS), and NTDs amongst patients receiving DTG are increased [24]. Consummate ubiquitous observed events were as follows: GI; diarrhoea in (35%), reduce appetite in (30%), abdominal pain in (21%) and nausea in (13%), respiratory; cough in (56%), pharyngeal pain in (35%), nasal congestion in (30%) and sinus congestion in (17%). Musculoskeletal; extremity pain in (26%), arthralgia in (13%) and back pain in (13%). General; fever in (30%), lymphadenopathy in (26%), headache in (26%) and dizziness in (17%) [3].

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**Drug interactions:** Dolutegravir is substantially metabolized via UDP glucuronyl transferase 1A1 (UGT 1A1), with minor input from cytochrome P450 3A4 (CYP3A4), which notes minimal DDI potential as a perpetrator drug. Both artemether (ARM) and lumefantrine (LF) are mainly metabolized via CYP3A4, CYP2B6, CYP2C9, and CYP2C19 to active metabolites dihydroartemisinic (DHA) and desbutyl-lumefantrine (DBL), respectively. Artesunate (AS) is a prodrug and substrate of CYP2A6 and undergoes fast hydrolysis to DHA, while amodiaquine (AQ) is extensively metabolized by CYP 2C8 to its active metabolite, N-de sethylamodiaquine (DEAQ). Concurrent administration of artemether-lumefantrine with inducers of CYP3A4 sequences in important minimizations in artemether and dihydroartemisinic exposures. Identically, clinically significant DDIs with ritonavir-boosted protease inhibitor ART regimens have been observed [25]. DTG is a substrate for Cytochrome-P450-3A4 (CYP3A4) and Uridine-diphosphate-glucuronosyltransferase-1A1 (UGT1A1). These enzymes are induced by rifampicin. The co-administration of DTG and rifampicin consequently leads to a reduction of DTG scales in the blood. Two folding the required daily dose of DTG is recommended for appropriate clinical efficacy [26].

| Concurrent medicine class: drug name | Effect on dolutegravir or concurrent medicine | Clinical recommendations |
|---|---|---|
| **HIV-1 antiviral agents** | | |
| NNRTI: etravirine [17] | ↓ dolutegravir | Avoid use with etravirine without coincident administration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir |
| NNRTI: efavirenz [17] | ↓ dolutegravir | ↑ dolutegravir dosage to 50 mg twice daily in management-naive or management-experienced INSTI naive patients; consider optional admixture for patients with potential INSTI-resistance |
| NNRTI: nevirapine [26] | ↓ dolutegravir | Avoid use with nevirapine; inadequate data to make dosing recommendations |
| Protease inhibitor: fosamprenavir/ritonavir and tipranavir/ritonavir [26] | ↓ dolutegravir | ↑ dolutegravir dosage to 50 mg twice daily in management-naive or management -experienced INSTI naive patients; thought-out optional admixture for patients with implicit INSTI-resistance |
| Other agents | | |
| CYP3A inducers (oxcarbazepine, phenytoin, phenobarbital, carbamazepine, St. John's wort) [17] | ↓ dolutegravir | Avoid concurrent use; inadequate data to make dosing recommendations |

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| | | |
|---|---|---|
| Rifampin [17] | ↓ dolutegravir | ↑ dolutegravir dosage to 50 mg twice daily in management-naive or management -experienced INSTI naive patients; consider optional combinations for patients with implicit INSTI-resistance |
| Polyvalent cation containing medications (eg, magnesium, aluminium, iron, calcium; antacids, iron supplements, oral supplements, buffered medications, antacids) [17, 26] | ↓ dolutegravir | Administer dolutegravir two hrs before or 6 hrs after receiving medications containing polyvalent cations |
| Sucralfate | ↓ dolutegravir | Administer dolutegravir 2 hours before or 6 hours after taking medications containing polyvalent cations |
| Metformin [17] | ↑ metformin | Monitor closely; a dose adjustment of metformin perhaps necessary |

**Table 1:** Established or potential drug interactions requiring dose or regimen alterations

**Pregnancy and breastfeeding profile of dolutegravir:** Dolutegravir has a suitable safety profile amongst older children, adolescents and adults, but a key concern has been the dearth of confirmation to help use in pregnancy and breastfeeding. Data from small cohorts of pregnant women who conceived while taking dolutegravir in Europe and North America revealed no confirmation of elevated birth defects. In Botswana, 1729 pregnant women who were induced on dolutegravir-based ART (of whom 280 were initiated in the 1st trimester) had no escalate in adverse foetal consequences when compared to 4593 pregnant women who were initiated on efavirenz-based regimens. However, consummate current data from Botswana suggests a possible elevated pitfall of neural tube defects in infants born to women who were initiated on dolutegravir prior to conception. In this preliminary analysis, 0.94% (4/426) of women taking dolutegravir gave birth to an infant with a NTD, analogized with 0.13% (14/11 173) of women taking non-dolutegravir-based regimens. Full sequences are anticipated in 2019, and pending more data, WHO recommend that women of childbearing age take optional ART regimens with better confirmation to assist safe use in pregnancy.

With respective to efficacy, pharmacokinetic data from 29 pregnant women receiving dolutegravir 50mg once daily resulted slightly lower maternal dolutegravir levels during the second and third trimesters, but this did not seem to impact greatly on viral outcomes or mother-to-child transmission. Confirmation from randomised clinical trials will be necessary to compare maternal and infant consequences including safety, pharmacokinetics and virological efficacy between dolutegravir and distinctive regimens. Two large trials have recently begun, but are only enrolling ART naïve pregnant women in the second and third trimesters. Therefore, surveillance of maternal and infant outcomes, particularly amongst women who conceive while receiving dolutegravir, will be important to confirm safety in pregnancy and whether dolutegravir can be recommended for use in women of child-bearing age.

## Conclusion

Dolutegravir (GSK1349572) is a potent inhibitor of the HIV-1 integrase that has shown good safety, tolerability, predictable pharmacokinetics and efficacy

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in treatment naïve and experienced adults in Phase III trials. Dolutegravir is hastily absorbed pursuing oral administration. The median maximum plasma concentration is reached 1.5–2.5 hours after oral intake with a mean $t1/_2$ of 12–15 hours, delivering feasible for once-daily dosing without the seek for pharmacological boosting. Bioavailability varies with fat content. Dolutegravir functions by interposing with an enzyme necessitated by HIV called integrase. Using Dolutegravir as section of combination therapy downgrades HIV's capability to infect cells and create copies of itself. The co-administration of DTG and rifampicin consequently leads to a reduction of DTG levels in the blood. Two folding the required daily dose of DTG is recommended for appropriate clinical efficacy.

## Abbreviations

ART: Antiretroviral therapy; DTG: Dolutegravir; FDA: Food and drug administration; WHO: World health organization; CYP3A4: Cytochrome-P450-3A4; HIV: Human immuno virus; INSTI: Integrase strand transfer inhibitor; NNRTI: Non-nucleoside reverse transcriptase inhibitor; TDF: Tenofovir; 3TC: Lamivudine; TLD: Tenofovir + Lamivudine + Dolutegravir; UGT1A1: Uridine-diphosphate-glucuronosyltransferase-1A1.

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**Data Sources:** Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, EMBASE, Scopus database, Scielo and Cochrane database. Search terms included: background, about pharmacokinetics, adverse drug reactions, drug-drug interactions and pregnancy and breast-feeding profile of dolutegravir.

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