

# HIV Treatment Clinical Brief: Dolutegravir

## INTRODUCTION

Dolutegravir (DTG) belongs to the class of antiretroviral medicines called integrase inhibitors (INIs) or integrase strand transfer inhibitors (INSTIs).

Integrase inhibitors work by blocking integrase, the enzyme required for HIV to insert its viral DNA into the DNA of a host CD4 cell. DTG is a well-tolerated antiretroviral that is effective at suppressing HIV, can be taken once a day, and has a high barrier to resistance. It is increasingly recognized as a potential first-line treatment option for HIV.

### US FDA-approved integrase inhibitors

**Dolutegravir (DTG; Tivicay®)**

**Elvitegravir (EVG; Vitekta®)**

**Raltegravir (RAL; Isentress®)**

## CLINICAL TRIALS

In clinical trials comparing DTG to other antiretroviral medicines, DTG was found to be as effective as the other drugs in the populations studied (see table below). A study using DTG among treatment-experienced patients with pre-existing integrase inhibitor resistance showed that

69% of patients had undetectable viral load at week 24.<sup>1</sup>



*Tablet sizes of efavirenz 600 mg (top) and 200 mg (middle) compared to dolutegravir 50 mg (bottom).*

Markings on the tablet, color, and design may differ among manufacturers.

## Clinical trials comparing dolutegravir with other drugs

Trial name	Drugs and regimens compared	Patient population	Results
SPRING-2 <sup>2,3</sup>	Dolutegravir vs. raltegravir	Treatment-naïve	At week 48, 88% on dolutegravir and 86% on raltegravir had viral suppression.
SAILING <sup>4</sup>	Dolutegravir vs. raltegravir	Treatment-experienced and failing therapy	At week 48, 71% on dolutegravir and 64% on raltegravir had viral suppression (P=0.03).
FLAMINGO <sup>5</sup>	Dolutegravir vs. darunavir	Treatment-naïve	At week 96, 80% on dolutegravir and 68% on darunavir had viral suppression (P=0.002).
SINGLE <sup>6</sup>	Dolutegravir with abacavir and lamivudine vs. efavirenz with tenofovir and emtricitabine	Treatment-naïve	At week 48, 88% on the dolutegravir combination and 81% on the efavirenz combination had viral suppression (P=0.003); 2% on dolutegravir had to stop treatment due to side effects or other adverse events compared to 10% on the efavirenz-containing regimen.
IMPAACT P1093 <sup>7</sup>	Dolutegravir with an optimized background regimen	Treatment-experienced 12- to 18-year-old adolescents	At week 48, 61% had viral suppression.
DAWNING <sup>8</sup>	Dolutegravir with 2 nucleoside reverse transcriptase inhibitors (NRTIs) vs. lopinavir/ritonavir (LPV/RTV) with 2NRTIs	Treatment-experienced adults failing first-line therapy of NNRTI + 2NRTIs	At week 24, 78% of subjects on dolutegravir vs. 69% on lopinavir/ritonavir achieved viral suppression. The Independent Data Monitoring Committee recommended discontinuation of the lopinavir/ritonavir arm (P <0.001).

In treatment-naïve women, a DTG plus abacavir (ABC) plus lamivudine (3TC) regimen provided statistically superior viral suppression (HIV-1 RNA <50 copies/mL) rates at week 48 compared to atazanavir boosted with ritonavir (ATV/r) plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC).<sup>9</sup>

## INDICATIONS

DTG is used for the treatment of HIV in combination with other antiretrovirals in adults and adolescents. It is a useful option for treatment-experienced patients because of its potency—its ability to control HIV levels in the body—even when there is resistance to other drugs in the treatment regimen. It is a recommended first-line treatment for HIV infection by the Department of Health and Human Services (DHHS), the European AIDS Clinical Society (EACS), and the International Antiviral Society-USA (IAS-USA). In its 2016 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, the World Health Organization (WHO) included DTG in alternative first-line antiretroviral therapy (ART) regimens (see table below).

## WHO 2016 preferred and alternative adult ART regimens

Preferred first-line regimens	Alternative first-line regimens
TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG TDF + 3TC (or FTC) + EFV400 TDF + 3TC (or FTC) + NVP

## REGULATORY APPROVALS AND DOSING

DTG was approved for use by the United States Food and Drug Administration (US FDA) in August 2013, and by the European Commission in January 2014.

## US FDA dolutegravir dosing

50 mg <i>once</i> daily for adults and adolescents over 12 years who weigh 40 kg and above, and who have not previously taken antiretrovirals before or have used other types of antiretrovirals, but never used an integrase inhibitor
50 mg <i>twice</i> daily for people who have used integrase inhibitors before and who have or are suspected to have resistance to other integrase inhibitors
50 mg <i>twice</i> daily for people who are taking any of these other drugs (regardless of whether there has been previous exposure to integrase inhibitors): efavirenz, rifampin, ritonavir-boosted fosamprevir, ritonavir-boosted tipranavir

## European Medicines Association dolutegravir dosing

Adult dosing	Adolescent dosing	
50 mg <i>once</i> daily for people without documented or clinically suspected resistance to integrase inhibitors	50 mg <i>once</i> daily for adolescents aged 12 to less than 18 years and weighing at least 40 kg without resistance to integrase inhibitors	
50 mg <i>twice</i> daily for people with documented or clinically suspected resistance to integrase inhibitors	<b>Children from 6 years to less than 12 years</b>	
	<b>Body weight (kg)</b>	<b>Dosing</b>
	15 to less than 20	20 mg <i>once</i> daily (taken as two 10 mg tablets)
	20 to less than 30	25 mg <i>once</i> daily
50 mg <i>twice</i> daily for people who are taking any of these other drugs: efavirenz, nevirapine, rifampin, ritonavir-boosted tipranavir	30 to less than 40	35 mg <i>once</i> daily (taken as one 25 mg tablet and one 10 mg tablet)
	40 or greater	50 mg <i>once</i> daily

## SIDE EFFECTS

In registration studies, DTG was better tolerated than efavirenz (EFV) or darunavir/ritonavir (DRV/r) and although there was an increased risk of insomnia, more serious central nervous system (CNS) side effects such as depression and suicidal ideation were rare.<sup>10</sup> Following marketing approvals, evidence from clinical practice has emerged suggesting that DTG is associated with a higher incidence of neuropsychiatric side effects than was observed in clinical trials. In a cohort study of 556 patients in the Netherlands, after a median follow up of 225 days, DTG was stopped in 15.3% of the patients. The reasons for stopping were intolerability, insomnia, sleep disturbance, gastrointestinal complaints, and neuropsychiatric symptoms, such as anxiety, psychosis, and depression.<sup>11</sup> The need to switch from DTG was observed to be more frequent when the ART regimen also contained abacavir (ABC).

A retrospective study of 1950 patients in Germany starting an integrase inhibitor between 2007 and 2016 estimated that the rate of any adverse event and neuropsychiatric adverse events leading to discontinuation within 12 months was 7.6% and 5.6% for DTG, 7.6% and 0.7% for EVG, and 3.3% and 1.9% for RAL. Neuropsychiatric adverse events leading to DTG discontinuation were observed more frequently in women, in patients older than 60 years, and in patients who were human leucocyte antigen (HLA)-B\*5701-negative who initiated ABC at the same time.<sup>12</sup>

## DRUG-DRUG INTERACTIONS

DTG can interact with some antiretrovirals and other medications. Dose adjustment or more frequent monitoring may be required.

Medicine	Interaction	Recommendation
Etravirine	Decreases the concentration of dolutegravir	Dolutegravir should not be used with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir.
Efavirenz	Decreases the concentration of dolutegravir	50 mg twice daily of dolutegravir is recommended in treatment-naïve or treatment-experienced, integrase inhibitor-naïve patients.
Nevirapine	Decreases the concentration of dolutegravir	Co-administration with nevirapine should be avoided.
Fosamprenavir/ritonavir, tipranavir/ritonavir	Decreases the concentration of dolutegravir	50 mg twice daily of dolutegravir is recommended in treatment-naïve or treatment-experienced, integrase inhibitor-naïve patients.
Oxcarbazepine, phenytoin phenobarbital, carbamazepine, St. John's wort	Decreases the concentration of dolutegravir	Co-administration with these metabolic inducers should be avoided.
Medications containing polyvalent cations: cation-containing antacids or laxatives, sucralfate, buffered medications	Decreases the concentration of dolutegravir	Dolutegravir should be administered 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins that contain calcium or iron	Decreases the concentration of dolutegravir	Dolutegravir should be administered 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, dolutegravir and supplements containing calcium or iron can be taken together with food.
Metformin	Increases the concentration of metformin	With concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or dolutegravir. When stopping dolutegravir, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of dolutegravir is recommended.
Rifampin	Decreases the concentration of dolutegravir	50 mg twice daily of dolutegravir is recommended in treatment-naïve or treatment-experienced, integrase inhibitor-naïve patients.

## CONTRAINDICATIONS

DTG is contraindicated in patients:

- with a previous hypersensitivity reaction to DTG
- receiving dofetilide (a class III antiarrhythmic agent), due to the potential for increased dofetilide plasma concentrations and associated serious and/or life threatening adverse events (such as QT prolongation and polymorphic ventricular tachycardia [torsade de points]).

## EVIDENCE GAPS<sup>13</sup>

**Pregnancy:** No patterns of anomalies have been observed across data sets reporting safety of DTG in pregnancy, including the Antiretroviral Pregnancy Registry (APR), The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC), DTG registration trials, and compassionate use programs. However, the small numbers in these datasets precludes firm conclusions. A study in Botswana of women initiating regimens with either EFV or DTG with TDF/FTC during pregnancy found no significant differences in birth outcomes by regimen.<sup>14</sup>

**Tuberculosis:** Information on treating HIV/TB coinfection with a DTG-based regimen is limited and related studies are ongoing or planned.

**Low- and Middle-Income Countries (LMICs):** DTG studies have included limited numbers of people in LMICs. All 624 participants of the DAWNING study are from LMICs, and 106 of these are from Asia. Several additional studies in LMICs are now under way (e.g., ADVANCE<sup>15</sup> and NAMSAL<sup>16</sup> in South Africa and Cameroon).

## ACCESS TO DOLUTEGRAVIR IN SOUTH AND SOUTHEAST ASIA

In April 2014, the Medicines Patent Pool (MPP) signed an agreement with DTG's originator company, ViiV Healthcare, to voluntarily license<sup>17</sup> the production and distribution of generic pediatric and adult formulations of the drug. The pediatric voluntary license<sup>18</sup> allows generic DTG to be sold in 121 named countries without requiring that a royalty be paid back to the originator. The adult license<sup>19</sup> allows DTG be sold in 92 countries, and to additional countries where a patent is not yet granted or where a compulsory license<sup>20</sup> has been issued. ViiV Healthcare-branded DTG is widely available in hospitals in China, Hong Kong SAR, Malaysia, Singapore, Taiwan, and Thailand.

South and Southeast Asian countries where only pediatric generic formulations can be marketed	South and Southeast Asian countries where both adult and pediatric generic formulations can be marketed
Malaysia, Sri Lanka, Thailand	Bangladesh, Bhutan, Cambodia, India, Indonesia, Laos, Myanmar, Nepal, Philippines, Vietnam

*A full list of countries where adult or pediatric generic DTG formulations can be marketed can be accessed from footnotes 18 and 19.*

Indian generic companies started producing and marketing this medicine in February 2017 under voluntary licenses from the MPP and ViiV Healthcare. The generic version has been priced at 2990 Indian Rupees (approximately US\$44.60<sup>21</sup>) for a supply of 30, 50 mg tablets on the private market in India (i.e., outside of government purchases). It is anticipated that larger-volume purchases to supply government-funded national HIV programs would drive down the price.

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18. Medicines Patent Pool Foundation Paediatric Sublicense Agreement. <http://www.medicinespatentpool.org/wp-content/uploads/MPPF-Sublicence-Paediatric-Execution-version-20140401.pdf>
19. Medicines Patent Pool Foundation Adult Sublicense Agreement. <http://www.medicinespatentpool.org/wp-content/uploads/ViiV-MPPF-Adult-Amended-and-Restated-Sublicence-Adult11.pdf>
20. Compulsory licensing is when a government allows a party other than the original patent holder to produce a previously patented product or process without the consent of the patent owner.
21. 1 USD=66.96 Indian Rupees. <https://www.rbi.org.in/> accessed February 14, 2017.