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.

Clinical trials comparing dolutegravir with other drugs

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Drugs and regimens compared</th>
<th>Patient population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRING-2</td>
<td>Dolutegravir vs. raltegravir</td>
<td>Treatment-naive</td>
<td>At week 48, 88% on dolutegravir and 86% on raltegravir had viral suppression.</td>
</tr>
<tr>
<td>SAILING</td>
<td>Dolutegravir vs. raltegravir</td>
<td>Treatment-experienced and failing therapy</td>
<td>At week 48, 71% on dolutegravir and 64% on raltegravir had viral suppression (P=0.03).</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>Dolutegravir vs. darunavir</td>
<td>Treatment-naive</td>
<td>At week 96, 80% on dolutegravir and 68% on darunavir had viral suppression (P=0.002).</td>
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<tr>
<td>SINGLE</td>
<td>Dolutegravir with abacavir and lamivudine vs. efavirenz with tenofovir and emtricitabine</td>
<td>Treatment-naive</td>
<td>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.</td>
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<tr>
<td>IMPAACT P1093</td>
<td>Dolutegravir with an optimized background regimen</td>
<td>Treatment-experienced 12- to 18-year-old adolescents</td>
<td>At week 48, 61% had viral suppression.</td>
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<tr>
<td>DAWNING</td>
<td>Dolutegravir with 2 nucleoside reverse transcriptase inhibitors (NRTIs) vs. lopinavir/ritonavir (LPV/RTV) with 2NRTIs</td>
<td>Treatment-experienced adults failing first-line therapy of NNRTI + 2NRTIs</td>
<td>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&lt;0.001).</td>
</tr>
</tbody>
</table>
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).

**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**

<table>
<thead>
<tr>
<th>Preferred first-line regimens</th>
<th>Alternative first-line regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + 3TC (or FTC) + EFV</td>
<td>AZT + 3TC + EFV (or NVP)</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC (or FTC) + DTG</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC (or FTC) + EFV400</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC (or FTC) + NVP</td>
</tr>
</tbody>
</table>

**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**

- **Adult dosing**
  - 50 mg once 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 twice daily for people who have used integrase inhibitors before and who have or are suspected to have resistance to other integrase inhibitors
  - 50 mg twice daily for people who are taking any of these other drugs (regardless of whether there has been previous exposure to integrase inhibitors): efavirenz, ritampin, ritonavir-boosted fosamprevir, ritonavir-boosted tipranavir

- **Adolescent dosing**
  - 50 mg once daily for adolescents aged 12 to less than 18 years and weighing at least 40 kg without resistance to integrase inhibitors

**European Medicines Association dolutegravir dosing**

<table>
<thead>
<tr>
<th>Adult dosing</th>
<th>Adolescent dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg once daily for people without documented or clinically suspected resistance to integrase inhibitors</td>
<td>50 mg once daily for adolescents aged 12 to less than 18 years and weighing at least 40 kg without resistance to integrase inhibitors</td>
</tr>
<tr>
<td>50 mg twice daily for people with documented or clinically suspected resistance to integrase inhibitors</td>
<td>Children from 6 years to less than 12 years</td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td><strong>Dosing</strong></td>
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<tr>
<td>15 to less than 20</td>
<td>20 mg once daily (taken as two 10 mg tablets)</td>
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<tr>
<td>20 to less than 30</td>
<td>25 mg once daily</td>
</tr>
<tr>
<td>30 to less than 40</td>
<td>35 mg once daily (taken as one 25 mg tablet and one 10 mg tablet)</td>
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<tr>
<td>40 or greater</td>
<td>50 mg once daily</td>
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</tbody>
</table>

**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. 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. 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.

**DRUG-DRUG INTERACTIONS**

DTG can interact with some antiretrovirals and other medications. Dose adjustment or more frequent monitoring may be required.
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 GAPS13
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.14

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., ADVANCE15 and NAMSAL16 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 license17 the production and distribution of generic pediatric and adult formulations of the drug. The pediatric voluntary license18 allows generic DTG to be sold in 121 named countries without requiring that a royalty be paid back to the originator. The adult license19 allows DTG to be sold in 92 countries, where a compulsory license20 has been issued. ViiV Healthcare-branded DTG is widely available in hospitals in China, Hong Kong SAR, Malaysia, Singapore, Taiwan, and Thailand.

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$44.6021) 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.
REFERENCES


10. Fit for Purpose, Antiretroviral treatment optimisation for adults and children, HIV i-Base, July 2017


13. Adapted from Fit for Purpose, Antiretroviral treatment optimisation for adults and children, HIV i-Base, July 2017


17. A voluntary license is an agreement that an originator company or a patent holder may make with other parties that provides the legal right to manufacture, import, and/or distribute the originator company’s pharmaceutical product.


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.