Therapeutics Research • Education • AIDS Training
TREATASIA
SNAPSHOTS
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HIV Treatment Snapshot: Dolutegravir

Dolutegravir (DTG) belongs to a class of antiretroviral medicines known as integrase inhibitors. It is used for the treatment of HIV in combination with other antiretrovirals in adults, adolescents, and older children. In its 2015 HIV treatment guidelines, the World Health Organization (WHO) included dolutegravir in alternative first-line antiretroviral therapy (ART) regimens. However, access to this drug is severely limited in the Asia-Pacific region due to the lack of availability of generic versions, and there is little data on its use in pregnant women.

U.S. FDA-approved integrase inhibitors

Dolutegravir (DTG; Tivicay®)
Raltegravir (RAL; Isentress®)
Elvitegravir (EVG; Vitekta®)

Dolutegravir has been increasingly recognized as a potential first-line option because of its limited side effect profile and high barrier to resistance. It is an especially valuable 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.

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.

REGULATORY APPROVALS

Dolutegravir was approved for use by the United States Food and Drug Administration (U.S. FDA) in August 2013, and by the European Commission in January 2014. Indian generic companies have obtained voluntary licenses from the originator company (ViiV Healthcare) and Medicines Patent Pool (MPP) to produce and market the drug. The generic form of the medication became commercially available in India in February 2017.

U.S. FDA dolutegravir dosing schedule

50 mg *once* daily for adults and adolescents over 12 years who weigh 40 kg and above, and who have not previously taken 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, rifampin, ritonavir-boosted fosamprevir, ritonavir-boosted tipranavir

European Medicines Association dolutegravir dosing schedule

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

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SAFETY AND EFFICACY

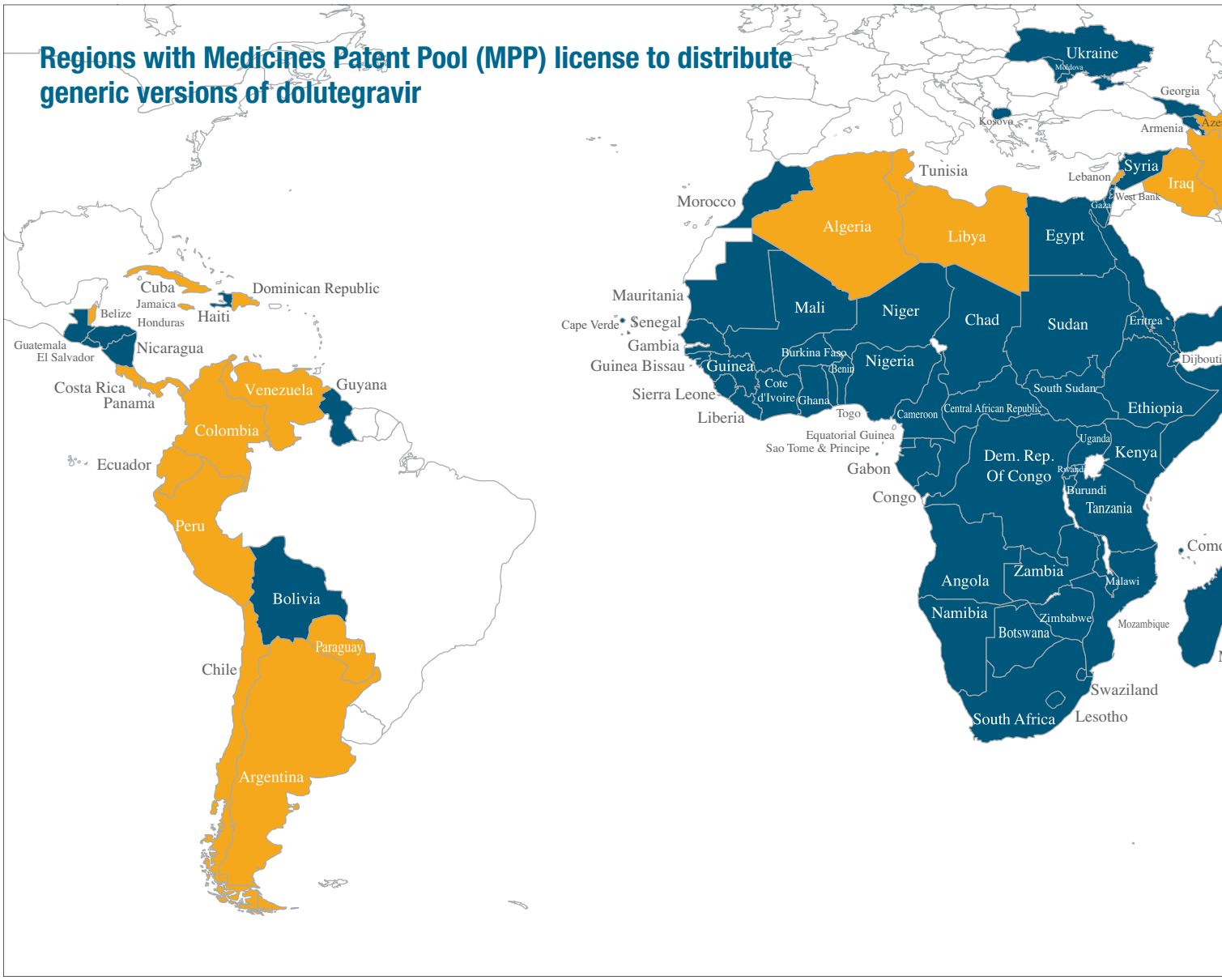
Dolutegravir is a well-tolerated antiretroviral that is effective at suppressing HIV and can be taken once a day. It has a high barrier to drug resistance, which means that it is harder for the virus to evolve in a way that makes the medicine less effective, which consequently reduces the risk of treatment failure.

A clinical trial of the two-drug combination of dolutegravir with lamivudine conducted in treatment-naïve adults showed that 90% of study participants had an undetectable HIV viral load (less than 50 copies per mL) at week 48.[1] Studies using dolutegravir among treatment-experienced patients with pre-existing integrase inhibitor resistance showed that 69% of patients had an undetectable viral load at week 24.[2] In clinical trials comparing dolutegravir to other antiretroviral medicines, dolutegravir was found to be as effective as the other drugs in the populations studied.

Clinical trials comparing dolutegravir with other drugs

Trial name	Drugs and regimens compared	Patient population	Results
SPRING-2[3,4]	Dolutegravir vs. raltegravir	Treatment-naïve	At week 48, 88% on dolutegravir and 86% on raltegravir had viral suppression.
SAILING[5]	Dolutegravir vs. raltegravir	Treatment-experienced and failing therapy	At week 48, 71% on dolutegravir and 64% on raltegravir had viral suppression.
FLAMINGO[6]	Dolutegravir vs. darunavir	Treatment-naïve	At week 96, 80% on dolutegravir and 68% on darunavir had viral suppression.

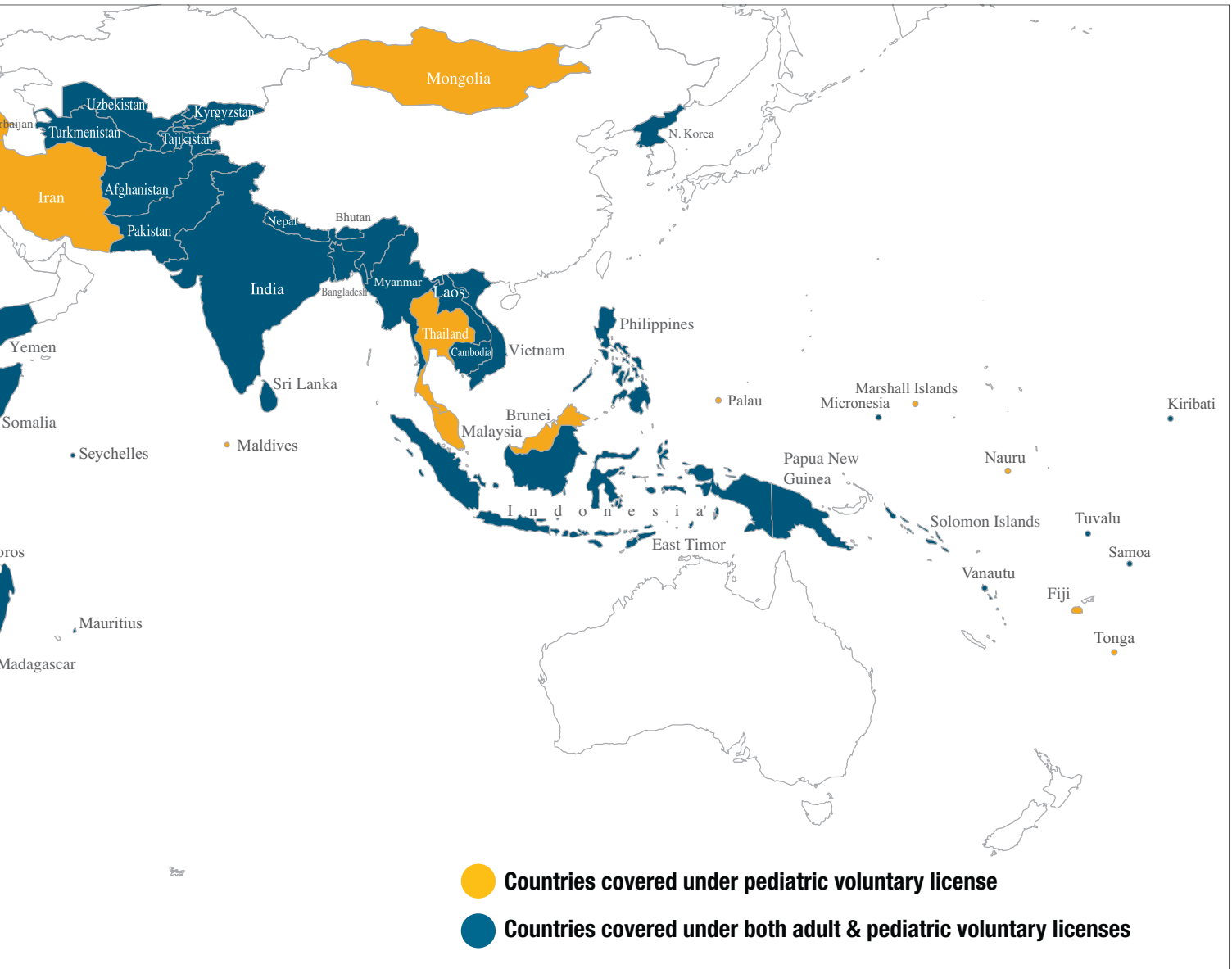
Regions with Medicines Patent Pool (MPP) license to distribute generic versions of dolutegravir



Trial name	Drugs and regimens compared	Patient population	Results
SINGLE[7]	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; 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[8]	Dolutegravir with an optimized background regimen	Treatment-experienced 12- to 18-year-old adolescents	At week 48, 61% had viral suppression.

VOLUNTARY LICENSES[9] TO GENERIC MANUFACTURERS

In April 2014, the Medicines Patent Pool (MPP) signed an agreement with dolutegravir's originator company, ViiV Healthcare, to voluntarily license the production and distribution of generic pediatric and adult formulations of the drug. The pediatric voluntary license[10] allows generic dolutegravir to be sold in 121 named countries without requiring that a royalty be paid back to the originator. The adult license[11] allows dolutegravir to be sold in 92 countries, and to additional countries where a patent is not yet granted or where a compulsory license[12] has been issued. The adult license is royalty-free in 82 countries; a 5-10% royalty fee is charged to the generic companies when dolutegravir is sold in 10 other countries. Generic companies that obtain a license from the MPP are also allowed to produce fixed-dose combinations (FDCs) of dolutegravir together with other antiretrovirals in a single tablet.



As of February 2017, 10 generic companies have sublicenses to produce dolutegravir under the MPP agreement, and one company has directly signed a bilateral voluntary license with the originator company.

PRICING AND ACCESS OPPORTUNITIES IN THE ASIA-PACIFIC REGION

Dolutegravir provides an option that could lead to a more simplified HIV drug regimen in the future. The generic version has been priced at 2990 Indian Rupees (approximately US$44.60[13]) 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 further drive down the price.

A number of countries in the Asia-Pacific region have been left out of the voluntary licenses, meaning that those countries are not guaranteed access to generic dolutegravir under these agreements. Countries can seek flexibilities under the TRIPS agreement[14] to facilitate drug access, such as compulsory licensing.

The MPP license also permits generic manufacturers to sell to countries not on the list if no patents have yet been granted in that country, even if patent applications are currently pending or in litigation.

While this is a substantial step forward compared to previous licenses, it remains a barrier for these countries for a few reasons. First, registering a generic medication with local regulators can be expensive, and generic companies may not be allowed to use some of the safety evidence produced by the originator when registering medications in countries not expressly covered by the license—leading to additional expense and uncertainty. Additionally, there may be little financial incentive for generic companies in this situation, since a pending patent could be approved while the regulatory approval process is underway or shortly thereafter. Moreover, some countries create legal liability for infringement during a patent-pending period if the patent is ultimately granted.

In order to expand access to dolutegravir, generic drug companies need to file standard drug registrations with the national drug regulators in each country. Regulators can help to make the drug more rapidly available by allowing dolutegravir producers to go through “fast track” processes for approving the registration applications.

Civil society advocates and community organizations can monitor the status of patent applications for dolutegravir and other medicines at http://www.medspal.org, which is coordinated and managed by the MPP. Additional information on national registrations is available through national drug regulatory and intellectual property offices.

1. Cahn P, et al. Dolutegravir-lamivudine as initial therapy in HIV-infected, ARV-naive patients: 48-week results of the PADDLE trial. AIDS 2016, Durban, South Africa, abstract 10270, July 2016.
2. Castagna A, et al. Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study, *The Journal of Infectious Diseases*, August 2014.
3. Francois R, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study, *The Lancet Infectious Diseases*, March 2013.
4. Francois R, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial, *The Lancet Infectious Diseases*, November 2013.
5. Cahn P, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study, *The Lancet*, August 2013.
6. Jean MM, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study, *The Lancet HIV*, April 2015.
7. Sharon W, et al. Dolutegravir plus abacavir/lamivudine for the initial treatment of HIV-1 infection, *The New England Journal of Medicine*, November 2013.
8. Rolando V, et al. Safety and efficacy of dolutegravir (DTG;GSK1349572) in treatment-experienced HIV-1 infected adolescents: 24-week results from IMPAACT P1093. IDWeek 2013, San Francisco, USA, abstract 172, October 2013.
9. 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.
10. Medicines Patent Pool Foundation Paediatric Sublicense Agreement http://www.medicinespatentpool.org/wp-content/uploads/MPPF-Sublicence-Paediatric-Execution-version-20140401.pdf.
11. Medicines Patent Pool Foundation Adult Sublicense Agreement http://www.medicinespatentpool.org/wp-content/uploads/Schedule-1-Form-of-Sublicence-to-Amended-and-Restated-ViiV-MPPF-Adult-....pdf.
12. 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. Compulsory licensing is incorporated into the World Trade Organization’s TRIPS Agreement.
13. 1 USD=66.96 Indian Rupees. https://www.rbi.org.in/ accessed February 14, 2017.
14. The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) is an international legal agreement between all the member nations of the World Trade Organization.

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